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ESTABILIDAD DIAGNÓSTICA DEL TRASTORNO BIPOLAR EN LA COMUNIDAD DE MADRID

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A todas aquellas personas que

padecen un trastorno bipolar

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1 RESUMEN

Los trastornos del humor o del estado del ánimo, desde el más bajo o melancolía al más alto o manía, han sido estudiados a lo largo de la historia humana. Desde la antigüedad hasta la época actual la patología bipolar, como hoy la entendemos, ha sido abordada con diferentes visiones. Respecto al trastorno bipolar se produce una paradoja: por un lado, es una enfermedad crónica y por tanto, una vez que se realiza el diagnóstico, se debería mantener estable a lo largo del tiempo y de su evolución; por otro lado, en la práctica clínica, es uno de los diagnósticos que con más frecuencia es modificado antes de estabilizarse de forma definitiva. La estabilidad diagnóstica se presenta como un criterio necesario para verificar un trastorno psiquiátrico y se relaciona con la validez predictiva de los diagnósticos psiquiátricos. El objetivo de este trabajo es realizar un estudio ecológico sobre la estabilidad diagnóstica del trastorno bipolar en seguimiento en los Centros de Salud Mental de la Comunidad de Madrid entre los años 1980 y 2009.

La importancia de la evaluación longitudinal se ha destacado a menudo para determinar la validez de los diagnósticos en psiquiatría. La estabilidad refleja la concordancia de los diagnósticos a lo largo del tiempo y puede determinarse a través de diferentes instrumentos. El trastorno bipolar genera una carga importante y, sin embargo, existe una alta prevalencia de diagnósticos erróneos que pueden contribuir en gran medida a aumentar los costes. En resumen, un número comparativamente pequeño de estudios han sido diseñados intencionadamente para revisar la relevancia de la estabilidad diagnóstica, tanto en el caso particular del trastorno bipolar como aplicada a las condiciones psiquiátricas generales. Los resultados de los estudios epidemiológicos existentes sobre el trastorno bipolar han mostrado una consistencia de moderada a alta en el diagnóstico de trastorno bipolar. Si bien estos estudios anteriores han proporcionado información detallada sobre la estabilidad diagnóstica de los trastornos bipolares, en términos generales están limitados por unos pocos puntos de evaluación y un breve tiempo de seguimiento. Además, el uso de intervalos de tiempo fijos predeterminados entre los puntos de evaluación puede haber contribuido a la aparición de sesgos de recuerdo. Dada la escasez de información sobre la estabilidad diagnóstica de los trastornos bipolares, se intentó evaluar su estabilidad a largo plazo en una gran muestra de población adulta que fue evaluada en múltiples puntos temporales, al menos diez durante al menos un año, en un contexto clínico de práctica habitual. Este estudio proporcionó una oportunidad única para arrojar luz sobre la cuestión de la estabilidad de los diagnósticos del trastorno bipolar a lo largo del tiempo y de cómo el grado de estabilidad diagnóstica puede influir en la práctica clínica, determinando así la carga de esta enfermedad. Se planteó la hipótesis de que la estabilidad en el tiempo de los trastornos bipolares podría diferir cuando se evalúan en múltiples puntos y durante un período de tiempo más largo, en comparación con los estudios anteriores.

El objetivo principal del presente estudio es realizar una evaluación ecológica de la estabilidad diagnóstica del trastorno bipolar en la Comunidad de Madrid. Otros objetivos de este estudio son determinar la consistencia temporal del diagnóstico, las variables personales que influyen en que éste se realice de forma estable y la prevalencia del trastorno bipolar en esta comunidad autónoma. Se postula la hipótesis de que existen dificultades para diagnosticar el trastorno bipolar y que su estabilidad diagnóstica se puede lograr con múltiples evaluaciones a lo largo de un período prolongado de tiempo. Se establece de forma arbitraria un 75% de coincidencia diagnóstica en las evaluaciones para considerar un diagnóstico como estable.

En este estudio se han recogido los datos aportados por el Registro Acumulativo de Casos de la Comunidad de Madrid, desde 1980 a 2009, en los Centros de Salud Mental de esta comunidad. Este registro recoge el conjunto mínimo básico de datos y utiliza códigos diagnósticos CIE. Se seleccionaron 14.557 pacientes que fueron diagnosticados al menos una vez de trastorno bipolar, que hubiesen tenido al menos 10 visitas durante el período de estudio y un mínimo de un año de seguimiento. Para estudiar la estabilidad diagnóstica se midieron dos índices complementarios: la consistencia temporal y la constancia diagnóstica (75% de las visitas con diagnóstico de trastorno bipolar). Se analizaron tanto la consistencia prospectiva como la consistencia retrospectiva, así como el coeficiente kappa de acuerdo diagnóstico entre la primera y la última evaluación. Para el análisis estadístico se empleó el programa *Statistical Package for the Social Sciences*, versión 27.0; se midió la consistencia temporal de los diagnósticos de trastorno bipolar y se comparó la prevalencia de diferentes diagnósticos psiquiátricos entre aquellos con trastorno bipolar estable. Los análisis estadísticos se realizaron en dos pasos para buscar los determinantes de la inestabilidad: análisis univariados seguidos de un análisis multivariante mediante regresión logística.

Un total de 14.557 pacientes fueron diagnosticados de trastorno bipolar, durante al menos una evaluación, recibieron al menos 10 visitas y tuvieron al menos un año de seguimiento. El 63,9% eran mujeres y el 36,1% varones. Hubo un total de 2.026 pacientes que fueron diagnosticados de trastorno bipolar en su primera y última evaluación. En la primera visita se diagnosticó a 3.988 pacientes un trastorno bipolar con una consistencia prospectiva del 50,8%. En la última visita se diagnosticó a 5.396 pacientes un trastorno bipolar con una consistencia retrospectiva del 37,5%. Por otro lado, el valor de kappa fue de 0,17. Una de las causas más frecuentes de confusión en el diagnóstico del trastorno bipolar son los diversos diagnósticos en la categoría F3 de trastornos afectivos no bipolares. La constancia diagnóstica del trastorno bipolar fue del 18,3%. Los pacientes con un diagnóstico estable de trastorno bipolar se diagnosticaron antes y precisaron un menor número de evaluaciones que aquellos que tenían un diagnóstico no estable; los que tenían un diagnóstico no estable requerían menos tiempo y menos visitas para que se les retirase este diagnóstico. Teniendo en cuenta únicamente los pacientes con un diagnóstico estable bipolar, se encontró una prevalencia del 0,4%. En la regresión logística realizada se relacionó significativamente el presentar un diagnóstico de trastorno bipolar estable o no con: el estado civil, el nivel educativo, la situación laboral y los antecedentes personales de asistencia psiquiátrica.

Este estudio abordó el tema de la estabilidad diagnóstica en el trastorno bipolar en la Comunidad de Madrid. Los resultados mostraron una estabilidad muy pobre según los métodos de estudio y notablemente inferior a la encontrada en estudios anteriores. En el conjunto de la muestra, sólo el 18,3% de los pacientes mantuvieron los diagnósticos de trastorno bipolar en el 75% de las evaluaciones y se encontró que las consistencias tanto prospectiva como retrospectiva eran bajas. Algunas razones metodológicas podrían explicar las diferencias con estudios anteriores, especialmente el escaso número de evaluaciones y el período de seguimiento más corto utilizado por éstos, que puede no dar tiempo suficiente para llegar al diagnóstico correcto. Nuestro estudio tiene las limitaciones derivadas del diseño metodológico de cualquier estudio naturalista retrospectivo y también está limitado por la posible existencia de vías no controladas de atención psiquiátrica, pero puede reflejar con mayor precisión el proceso clínico "real", lo que pone en entredicho la precisión de los sistemas de evaluación clínica en condiciones de práctica clínica habitual. La prevalencia del trastorno bipolar en esta muestra psiquiátrica, del 0,4%, fue menor que la encontrada en otras poblaciones psiquiátricas, pero cercana a estudios más precisos. El estudio más detallado de los factores que influyen en la estabilidad del trastorno bipolar y un mejor conocimiento del curso de los diagnósticos a lo largo de su evolución se proponen como dos futuras líneas de investigación.

Aunque se hallaron algunos factores relacionados con la estabilidad diagnóstica del trastorno bipolar, son necesarios nuevos trabajos que estudien estas variables para facilitar la identificación de estos pacientes y realizar un diagnóstico acertado al inicio de la enfermedad. Se sugiere que para futuros estudios sobre el trastorno bipolar se tenga en cuenta que el diagnóstico sea estable, y no se incluyan a pacientes con un diagnóstico realizado transversalmente que puedan falsear los resultados. En las investigaciones futuras sobre el trastorno bipolar se deben incluir estudios prospectivos de seguimiento y ensayos clínicos para que este campo pueda avanzar. Los clínicos necesitan herramientas diagnósticas fiables para reducir los errores diagnósticos en el trastorno bipolar.

2 INTRODUCCIÓN

Resumen

Los trastornos del humor o del estado del ánimo, desde el más bajo o melancolía al más alto o manía, han sido estudiados a lo largo de la historia humana. Desde la antigüedad hasta la época actual la patología bipolar, como hoy la entendemos, ha sido abordada con diferentes visiones. Respecto al trastorno bipolar se produce una paradoja: por un lado, es una enfermedad crónica y por tanto, una vez que se realiza el diagnóstico, se debería mantener estable a lo largo del tiempo y de su evolución; por otro lado, en la práctica clínica, es uno de los diagnósticos que con más frecuencia es modificado antes de estabilizarse de forma definitiva. La estabilidad diagnóstica se presenta como un criterio necesario para verificar un trastorno psiquiátrico y se relaciona con la validez predictiva de los diagnósticos psiquiátricos. El objetivo de este trabajo es realizar un estudio ecológico sobre la estabilidad diagnóstica del trastorno bipolar en seguimiento en los Centros de Salud Mental de la Comunidad de Madrid entre los años 1980 y 2009.

2.1 REVISIÓN HISTÓRICA DEL TRASTORNO BIPOLAR

Los trastornos del humor o del estado estado del ánimo, desde el más bajo o melancolía al más alto o manía, han sido estudiados a lo largo de la historia humana. Ya en la antigüedad, la presencia ambos estados de ánimo era evidente y se describían en la literatura. El término melancolía proviene del griego ("melas", negro, y "chole", bilis); sin embargo, el origen del término "manía" es mucho menos claro (Mason et al. 2016).

A continuación, se presenta un breve recorrido sobre las reseñas más significativas a lo largo de la historia hasta llegar al concepto actual de trastorno bipolar.

2.1.1 Antigüedad

Para Hipócrates de Cos (460–337 a. C.) la melancolía describía un estado patológico de tristeza severa debido al acúmulo de bilis negra (Angst et Marneros 2001); un estado opuesto era el resultado de un exceso de bilis amarilla (Laios et al. 2004).

Sorano de Éfeso (98-138 d. C.) distinguió la melancolía de la manía, éstas eran dos entidades distintas pero que compartían síntomas. Conceptuaba la manía como un trastorno del entendimiento, se observaba más frecuentemente en hombres jóvenes, con un curso continuo o intermitente y cuyas manifestaciones clínicas eran "cólera o furor, alborozo, tristeza y angustia" (Chinchilla et al. 2008).

Areteo de Capadocia (siglo I d. C.) fue el primero que vinculó estos dos estados de manía y melancolía, creyendo que la melancolía y la manía tienían la misma etiología de disfunción cerebral (Angst et Marneros 2001).

Galeno de Pérgamo (130-210 d. C.) estableció firmemente la melancolía como una enfermedad crónica y recurrente (Parker et Hadzi-Pavlovic 1996).

2.1.2 Edad Media

Alejandro de Tralles (525-605) reflejó que no siempre la tristeza o el temor son los síntomas característicos de los pacientes melancólicos, sino que, en otras ocasiones prevalece en ellos la hilaridad, la ira y la ansiedad, fenómenos cercanos a los estados maníacos (Laín Entralgo 1978).

Avicena (980-1037), en el año 1000 escribe: «indudablemente, el material que produce la manía es de la misma naturaleza que el que produce la melancolía». Concibe una forma especial de melancolía sobrevenida de la mezcla de la bilis negra con la flema dando una caracterización acinética-catatónica de la enfermedad (Burton 1947).

2.1.3 Psiquiatría francesa

Desde la antigüedad hasta el siglo XIX, la manía y la melancolía se consideraron dos trastornos completamente diferentes que abarcaban una amplia variedad de síndromes psiquiátricos. Jean-Pierre Falret (1794-1870) creó el primer concepto de un trastorno psiquiátrico nuevo y separado que abarcaba tanto la manía como la depresión y publicó su descripción de esta enfermedad en 1851, que denominó "locura circular", un trastorno mental caracterizado por un ciclo continuo de depresión, manía e intervalos libres de duración variable entre estos dos extremos (Angst et Marneros 2001; Angst 2002).

Jules Baillarger (1809-1890) describió la "locura de doble forma", en la que la manía y la melancolía se transforman una en otra, pero sin necesidad de un intervalo libre entre ambos, en contraste con la descripción de Falret, que incluiría a los que tienen un intervalo largo entre los dos estados de ánimo (Angst et Marneros 2001).

2.1.4 Psiquiatría Alemana

Karl Ludwig Kahlbaum (1828-1899) hablaba de "vesania típica circular" al referirse a estos trastornos episódicos melancólicos y maníacos. Además incluyó después formas menores más leves, a las que denominó ciclotimia, caracterizadas por episodios tanto de depresión como de excitación pero que no terminaban en demencia, como podían hacerlo la manía o melancolía crónicas. También acuñó el término distimia para referirse a una variedad crónica de melancolía (Angst 2002).

Emil Kraepelin (1856-1926) introdujo el concepto de "locura maníaco-depresiva" como entidad nosológica independiente en contraposición a la "demencia precoz", posterriormente denominada esquizofrenia (Angst et Marneros 2001; Angst 2002).

Karl Leonhard (1904-1988), en las psicosis fásicas, incluye las psicosis maníaco-depresivas, la melancolía pura, la manía pura, las depresiones puras y las euforias puras. Por otro lado, las psicosis cicloides se posicionan entre los trastornos afectivos y la esquizofrenia (Peralta et al. 2007).

2.1.5 DSM-III

En 1980, el término de trastorno bipolar reemplaza al de trastorno maníaco-depresivo como término diagnóstico en el DSM-III (APA 1980). Se enfatizó en la polaridad del estado de ánimo en esta caracterización y que la presencia de cualquier manía indica trastorno bipolar (Ghaemi 2013).

2.1.6 DSM-IV

La hipomanía se puede diagnosticar ahora de forma episódica, ya que el episodio hipomaníaco tiene los mismos criterios de síntomas que el episodio maníaco, pero ahora sólo necesita durar 4 días y es claramente diferente del estado de ánimo no deprimido (APA 1994). Se clasifican los siguientes trastornos bipolares:

F30.x Trastorno bipolar I, episodio maníaco único
F31.0 Trastorno bipolar I, episodio más reciente hipomaníaco
F31.x Trastorno bipolar I, episodio más reciente maníaco
F31.6 Trastorno bipolar I, episodio más reciente mixto
F31.x Trastorno bipolar I, episodio más reciente depresivo
F31.9 Trastorno bipolar I, episodio más reciente no especificado
F31.8 Trastorno bipolar II
F34.0 Trastorno ciclotímico
F31.9 Trastorno bipolar no especificado

2.1.7 Espectro bipolar

El concepto de espectro en Física indica la aparente diversidad cualitativa de un continuo cuantitativo; por ejemplo, al hacer incidir un haz de luz blanca sobre un prisma y éste se descompone en una serie de colores ordenados según sus longitudes de onda.

La visión como espectro de los trastornos del estado de ánimo adopta un enfoque dimensional en el que los tipos de disfunción del estado de ánimo existen en un continuo y la gravedad se clasifica en función de los síntomas asociados (Benazzi 2006).

Hagop Akiskal detalla este concepto y propone que una ampliación de los criterios diagnósticos para los trastornos del estado de ánimo captaría mejor las vicisitudes que se observan en la presentación clínica (Akiskal et Pinto 1999). Utilizando sus caracterizaciones, el espectro de la enfermedad bipolar abarcaba manifestaciones más amplias de la enfermedad bipolar:

- Bipolar ½: Trastornos Esquizoafectivos.
- Bipolar I: Depresiones alternando con manías.
- Bipolar I y ½: Depresiones alternando con hipomanías prolongadas.
- Bipolar II: Depresiones alternando con hipomanías.
- Bipolar II y ½: Depresiones alternando con hipomanías breves (2 ó 3 días).
- Bipolar III: Hipomanía asociada a tratamiento antidepresivo, fotoluminoterapia y TEC.
- Bipolar III y ½: Bipolaridad asociada a adicciones (alcohol, estimulantes).
- Bipolar IV: Depresiones tardías asentadas sobre un temperamento hipertímico.

Bajo estas descripciones más amplias de los trastornos bipolares, se estima que entre el 4% y el 5% de la población general presentaría un diagnóstico de este espectro, lo que representa un aumento con respecto al 1% de la población general comúnmente citado según los criterios del DSM (Akiskal 2000).

Introduciendo enfoques más dimensionales, incluyendo dimensiones que

atraviesan las categorías actuales, Jules Angst presenta un modelo de espectro de síndromes del estado de ánimo que integra tres dimensiones (Angst et al. 2015) (Figura 1):

- Gravedad: desde los síntomas del estado de ánimo en sujetos normales, pasando por los síndromes de subumbral menor a umbral mayor y finalmente psicótico.
- Un espectro de síndromes cualitativos: desde la depresión hasta la manía, pasando por los subgrupos bipolares.
- Rasgos y trastornos de personalidad/temperamento asociados con el espectro de síndromes.

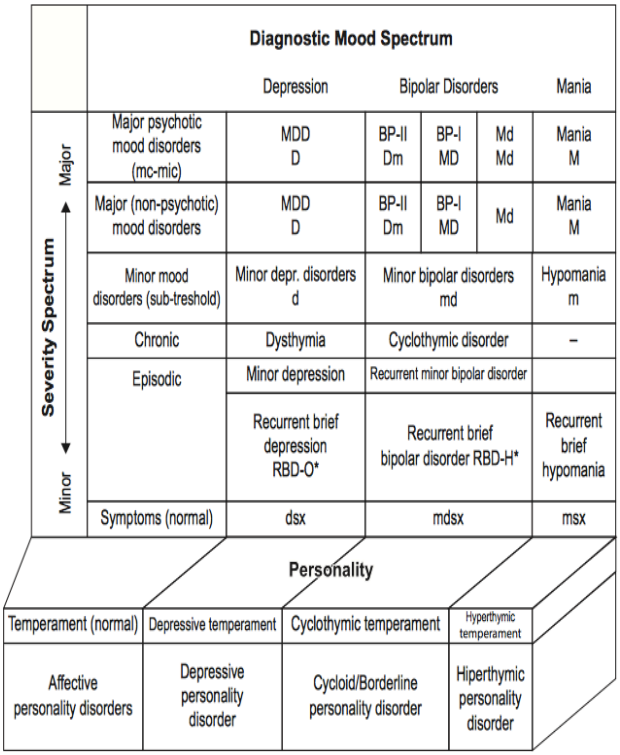

Figura 1. Modelo tridimensional del espectro de trastornos afectivos.
Tomado de Angst 2015.

2.2 DEFINICIÓN DE ESTABILIDAD DIAGNÓSTICA

La estabilidad diagnóstica se presenta, en un artículo que Robins y Guze publicaron en 1970, como un criterio necesario para verificar un síndrome psiquiátrico y la relacionan, por vez primera, con la validez predictiva de los diagnósticos psiquiátricos (Robins et Guze 1970). En otros trabajos más recientes, se define la estabilidad diagnóstica como la medida en la que un diagnóstico es confirmado en evaluaciones consecutivas (Fennig et al. 1994; Kim-Cohen et al. 2003). Como a día de hoy no disponemos de marcadores biológicos objetivables para el diagnóstico de entidades nosológicas en Psiquiatría, la estabilidad diagnóstica a lo largo del tiempo se ofrece como una medida fiable para validar diagnósticos psiquiátricos; también representa una medida útil para predecir el curso de un trastorno (Whitty et al. 2005). Por tanto, el estudio de la estabilidad de los diagnósticos puede proporcionar un soporte para un tratamiento óptimo de los pacientes. Y al revés, cuando no existe una estabilidad diagnóstica para una determiada patología, esto puede suponer importantes deficiencias en el tratamiento y evolución de la enfermedad.

Es habitual que se observe una inestabilidad en los diagnósticos psiquiátricos. Esto es debido a múltiples causas; entre ellas, Spitzer señala la varianza propia del sujeto, la varianza en la información recogida, la varianza

en la observación y la varianza en los criterios diagnósticos (Spitzer et al. 1975). Otra causa de la inestabilidad diagnóstica se debe a un factor intrínseco de las enfermedades mentales como es la evolución natural de las mismas. En el caso del trastorno bipolar, se trata de una patología que tiene una presentación variable a lo largo de su evolución. Además, en el trastorno bipolar se observan una multiplicidad de patrones de enfermedad que determinan una gran variabilidad interindividual.

Hay que tener en cuenta que el trastorno bipolar se caracteriza por una presentación en fases de diferente polo y graduadas en gravedad (Sánchez González et al 1998). Así, podemos observar, diversas fases del trastorno bipolar:

- Manía.
- Hipomanía.
- Depresión.
- Fase mixta, con síntomas maníacos y depresivos.

Esta variabilidad sintomática en la presentación clínica del trastorno bipolar a lo largo de su evolución constituye una desventaja a la hora de realizar un diagnostico acertado. Tanto es así que, siguiendo los postulados de algunos autores (Akiskal 2000; Angst 1995), se defiende una ampliación del propio concepto de trastorno bipolar y los criterios diagnósticos se expanden hasta abarcar todo un espectro bipolar. En este sentido, lo más aceptado es considerar a la patología bipolar como un trastorno, como así aparece en la Clasificación Internacional de Enfermedades en su 10ª revisión (CIE-10) (WHO 1992). Siguiendo la definición de trastorno bipolar de la CIE-10, debe haber al menos dos episodios del estado de ánimo entre los cuales al menos uno es un episodio hipomaníaco o maníaco (WHO 1992).

Existen diferentes métodos para aumentar la estabilidad de un diagnóstico, a pesar de que no presentan una fiabilidad aceptable para conseguirlo. La observación longitudinal se ha mostrado como un mejor método diagnóstico que la evaluación transversal, sobre todo en trastornos afectivos (Chen et al. 1998; Marneros et al. 1991). Ante la ausencia de marcadores objetivables de enfermedad en los trastornos mentales, la investigación en estudios genéticos puede ser una herramienta diagnóstica avanzada (Taylor 1992). También se ha postulado como un apoyo diagnóstico el tener en cuenta la respuesta al tratamiento (Blacker et Tsuang 1992). Otro método sería evaluar la función psicosocial y cómo se ve afectada por la enfermedad mental (Goodwin et Jamison 1990).

Existen pocos estudios centrados en el estudio de la estabilidad diagnóstica de los trastornos mentales en adultos, a pesar de que en los últimos años un número significativo de trabajos se han interesado en este tema (Fenning et al. 1994; Whitty et al. 2005; Chen et al. 1998; Baca-Garcia et al. 2007). De todos ellos, sólo un número reducido se ha enfocado en el trastorno bipolar (Chen et al. 1998; Baca-Garcia et al. 2007[2]; Kessing 2005; Rice et al. 1986; Weeke 1984). En la literatura, se encuentran más estudios centrados en la estabilidad diagnóstica de los primeros episodios psicóticos (Fenning et al. 1994; Whitty et al. 2005; Schwartz et al. 2000; Rufino et al. 2005; Amin et al. 1999; Jørgensen et al. 1997; Schimmelmann 2005; Veen et al. 2004; Addington et al. 2006).

Respecto al trastorno bipolar se produce una paradoja: por un lado, es una enfermedad crónica y por tanto, una vez que se realiza el diagnóstico, se de debería mantener estable a lo largo del tiempo y de su evolución; por otro lado, en la práctica clínica, es uno de los diagnósticos que con más frecuencia es modificado antes de estabilizarse de forma definitiva (Chen et al. 1998). En las fases tempranas del trastorno bipolar es cuando más complicado es realizar un diagnóstico certero, más si cabe si los primeros episodios son depresivos. Habitualmente no se alcanza un diagnóstico seguro si no es con un seguimiento longitudinal prolongado de los pacientes. Lo más habitual, cuando se realiza un cambio diagnóstico desde el trastorno bipolar, es que sea hacia un diagnóstico del espectro de la esquizofrenia (Kessing 2005; Schwartz et al. 2000).

Hay diversas circunstancias propias del trastorno bipolar que favorecen la inestabilidad en el diagnóstico:

a. La fenomenología presente el trastorno bipolar puede ser cambiante con el transcurrir del tiempo y no es patognomónica del mismo (Beiser et al. 2007). Las fases depresivas o maníacas pueden cursar con síntomas psicóticos y, estos episodios, se pueden diagnosticar erróneamente como episodios psicóticos en el contexto de otras enfermedades como la esquizofrenia.
b. Se han reportado que las tasas de error diagnóstico entre el trastorno depresivo mayor y el trastorno bipolar son sustanciales. La consecuencia de dicho diagnóstico erróneo habitualmente es un retraso

en el diagnóstico del trastorno bipolar, en algunos casos es un retraso de entre 8 y 10 años. (Hirschfeld et al. 2003; Baldessarini et al. 1999; Vöhringer et al. 2016). En los pacientes que las primeras fases del trastorno bipolar son depresivas, el diagnóstico se difiere hasta que ocurre una fase del polo maníaco que determina el diagnóstico bipolar.

c. La presencia de otro trastorno mental comórbido puede influir en la expresión sintomatológica de los fenómenos bipolares (Blacker et al. 1992; Kendler 1990). La presentación sintomática de fases bipolares en los pacientes que tienen un trastorno mental de otro tipo (ansiedad, obsesivo-compulsivo, de personalidad…) comórbido con el trastorno bipolar se puede ver distorsionada por la coexistencia de diferentes síntomas de los distintos trastornos.
d. Puede haber una inconsitencia diagnóstica interobservador (Cooper 1967). El diagnóstico en psiquiatría, se realiza a través de la entrevista clínica y la exploración psicopatológica; por lo cual, el diagnóstico depende de la subjetividad del entrevistador y, por tanto, es habitual que la consistencia interevaluador en psquiatría no sea de alta coincidencia.
e. Hay que tener en cuenta que las características sociodemográficas individuales pueden modificar el curso natural de la enfermedad bipolar (Schwartz et al. 2000). Las diferencias de género, etarias, culturales, educacionales, etc. determinan una plasticidad en la presentación fenomenológica de la sintomatología de los episodios afectivos bipolares.

Por todo ello, es de interés la investigación de los determinantes que influyen en la estabilidad diagnóstica del trastorno bipolar, los factores que determinan que se cambie el diagnóstico de trastorno bipolar a otro diagnóstico psiquiátrico o a la inversa, de otro trastorno al bipolar.

En otras ramas de la medicina, los diagnósticos suelen estar respaldados por la identificación de los procesos biológicos subyacentes, pero los diagnósticos psiquiátricos se basan solo en síndromes clínicos (Spitzer 1975). En ausencia de una sintomatología biológica objetiva del trastorno, la estabilidad en el tiempo representa la mejor prueba para validar el diagnóstico de trastorno bipolar y, en gran medida, puede usarse para predecir el curso del trastorno (Chen et al. 1998). Por esta razón, el estudio de la estabilidad diagnóstica del trastorno bipolar puede servir como base para el tratamiento terapéutico de los pacientes. Por el contrario, la ausencia de estabilidad en un diagnóstico puede generar un impacto grave (Marneros et al. 1991). Por ejemplo, el infradiagnóstico de trastorno bipolar conduce a un retraso del tratamiento o un tratamiento ineficaz (Taylor 1992). El sobrediagnóstico también puede tener consecuencias personales y sociales adversas, incluida la exposición innecesaria a los riesgos de la medicación, las oportunidades perdidas para el tratamiento de otras afecciones o los efectos sobre la actividad laboral (Blacker et al. 1992). Se estima que la tasa de pacientes bipolares que reciben diagnósticos inadecuados en los centros de salud mental varía entre un 20-60% (Goodwin et Jamison 1990; Baca-Garcia et al. 2007; Baca-Garcia et al. 2007[2]).

Hay un número limitado de estudios centrados en la estabilidad diagnóstica; aunque su número ha aumentado en los últimos años. La mayoría de ellos se centran en el primer episodio de psicosis y, en particular, en la consistencia posterior de los diagnósticos de esquizofrenia (Kessing 2005). Sin embargo, hay menos estudios centrados en la consistencia diagnóstica de trastorno bipolar a lo largo del tiempo. Para la validez diagnóstica en los trastornos psiquiátricos es esencial una consistencia en el tiempo, y debido a las posibles implicaciones del tratamiento, los cambios en el diagnóstico son un tema importante a considerar (Rice et al. 1986; Weeke 1984). En el caso del trastorno bipolar, hay resultados contradictorios en la literatura. Algunos estudios sugieren niveles moderados a altos de estabilidad diagnóstica temporal de trastorno bipolar (Weeke 1984; Schwartz et al. 2000; Rufino et al. 2005; Amin et al. 1999). Sin embargo, el diagnóstico inicial de trastorno bipolar a menudo es problemático con un retraso en el diagnóstico de 8 a 10 años, y los estudios con evaluaciones longitudinales repetidas ponen en duda la estabilidad de este diagnóstico en la práctica real (Mojtabai et al. 2003; Jørgensen et al. 1997; Schimmelmann 2005; Veen et al. 2004; Baldessarini et al. 1999; Baca-Garcia et al. 2007[2]).

En los estudios que analizan la estabilidad del diagnóstico de trastorno bipolar se ha utilizado habitualmente la clasificación DSM-IV; aunque se han encontrado tres estudios donde se ha utilizado la CIE-10 (Kim 2008; Kessing 2005; Amin et al. 1999). En alguno de los trabajos publicados se ha encontrado una estabilidad diagnóstica entre moderada y alta, aunque gran parte de los hallazgos que describen se ven limitados o bien por un número reducido de valoraciones a lo largo del período de estudio, o bien por un tiempo de seguimiento de los pacientes insuficiente (Fennig et al. 1994; Weeke 1984; Schwartz et al. 2000; Rufino et al. 2005; Schimmelmann et al. 2005; Veen et al. 2004; Addington et al. 2006; Lenz et al. 1991; Fraguas et al. 2007). Otros estudios no presentran estas limitaciones (Chen et al. 1998; Marneros et al. 1991; Baca-Garcia et al. 2007[2]; Weeke 1984; Bromet et al. 2011).

Los diagnósticos de trastornos psiquiátricos, incluido el trastorno bipolar, se basan principalmente en una evaluación longitudinal de diversas presentaciones clínicas transversales. El trastorno bipolar es un trastorno mental crónico y severo, caracterizado por episodios recurrentes de depresión (estado de ánimo bajo), manía o hipomanía (estados de ánimo elevados) y estado de ánimo mixto. Además, dado que se considera una enfermedad de por vida, el diagnóstico de trastorno bipolar, una vez establecido, debe ser estable en el tiempo (Kim-Cohen et al. 2003). Sin embargo, este no es siempre el caso en la práctica clínica (Whitty et al. 2005).

Existen, por tanto, razones relevantes para realizar nuevas investigaciones sobre la estabilidad diagnóstica del trastorno bipolar:

- Aunque la prevalencia más ampliamente aceptada del trastorno bipolar se encuentra en un 1-2% de la población (Sajatovic 2005; Weissman et al. 1996), nuevos estudios sobre el trastorno bipolar tipo I muestran unas prevalencias mayores (Kessler et al. 2005; Bijl et al. 1998; ten Have et al. 2002; Grant et al. 2005; Angst 1998). Incluso algunos estudios aproximan la prevalencia al 5% cuando se amplian los criterios hasta conformar lo que se ha dado en llamar espectro bipolar (Dunner 2003; Hirschfeld 2001; Carta et Angst 2007). En este caso, se trataría de una patología infradiagnosticada y, por tanto, un elevado número de pacientes no recibirían tratamiento o tendrían prescrito un tratamiento inadecuado para su trastorno.
- Algunos estudios han identificado errores fercuentes para realizar el diagnóstico del trastorno bipolar (Hirschfeld et al. 2003; Lish et al. 1994; Ghaemi et al. 1999; Angst et al. 2002, Berk et al. 2006). Estos errores, en la primera valoración, están entre un 48% y un 69%, según la *National Depressive and Manic-Depressive Association* (Hirschfeld et al. 2003; Lish et al. 1994). Por otro lado, están los estudios que ponen de manifiesto el retraso diagnóstico en el trastorno bipolar y el subsecuente retraso de un tratamiento adecuado (Mojtabai et al. 2003; Jørgensen et al. 1997; Schimmelmann 2005; Veen et al. 2004; Baldessarini et al. 1999). Esto supone que un alto porcentaje de pacientes con trastorno bipolar reciben un diagnóstico erróneo y un tratamiento inadecuado durante los primeros años de evolución de la enfermedad. Así, además de perder la oportunidad de establecer un correcto tratamiento dirigido a prevenir las recaídas del trastorno bipolar, se aumenta el número de años vividos con discapacidad.
- Varios estudios han encontrado que el diagnóstico precoz de trastorno bipolar está asociado a un mejor pronóstico: mejoría clínica que determina una mejor calidad de vida, los beneficios propios de un comienzo precoz un tratamiento adecuado, evitar los efectos indeseados de un tratamiento inapropiado y la disminución del riesgo de suicidio asociado al trastorno bipolar (Berk et al. 2006). Para paliar este infradiagnóstico cuando se evaluan inicialmente los episodios depresivos se ha propuesto utilizar herramientas de cribado que ayuden a un diagnóstico precoz del trastorno bipolar (Dunner 2003; Hirschfeld et al. 2003). Cuando no se diagnostica un trastorno bipolar en las evaluaciones iniciales se producen un aumento de complicaciones a lo largo de la evolución, como mayores tasas de suicidio, de trastornos por abuso de drogas y las propias de la iatrogenia de un tratamiento inadecuado. Además, se produce una pérdida de la calidad de vida, aumenta la carga económica de la enfermedad (Dunner 2003) y hace que el trastorno bipolar presente el mayor porcentaje de suicidio dentro de los trastornos psiquiátricos (Chen et Dilsaver 1996; Tondeo et al. 2003). El trastorno bipolar puede tener un

importante impacto en la capacidad de funcionamiento de un individuo y se asocia con un riesgo de suicidio a largo plazo (Moore et al 2012).

- Según el estudio *Global Burden of Disease 2013*, el número de casos de trastorno bipolar aumentó en un 50% en los últimos 20 años, alcanzando 50 millones de casos y se clasificó como la 16ª causa principal de años vividos con discapacidad en 2013 (Ferrari et al. 2013). El trastorno bipolar representa 9,9 millones de años ajustados vividos con discapacidad en 2013, lo que explica el 0.4% de los años ajustados vividos con discapacidad total. Se han encontrado 5,5 millones de años ajustados vividos con discapacidad para mujeres y 4,4 millones para hombres. Los años ajustados vividos con discapacidad fueron evidentes a partir de los 10 años, alcanzan su punto máximo a los 20 años y posteriormente disminuyeron.
- Los pacientes con trastorno bipolar frecuentemente presentan comorbilidades, tanto de patologías orgánicas como de otros trastornos mentales (McElroy 2004). La comorbilidad con otros trastornos psiquiátricos se estima por encima del 50% para el suptipo I. Entre estas comorbilidades, las más altas son con los trastornos por abuso de sustancias (48-71%) y los trastornos de ansiedad (42-93%) (Vieta et al. 2001). Además, estos trastornos, cuando están descompensados, provocan un aumento de la sintomatología de los otros trastornos comórbidos. Así, un paciente con una depresión bipolar suele tener un aumento de los síntomas de ansiedad. De igual manera, un paciente bipolar con una manía aguda incrementa el riesgo de consumo de sustancias.

Es necesario constatar que el estudio que se presenta en este trabajo doctoral se enmarca dentro de un proyecto general de la Comunidad de Madrid para crear una base de datos que recojan las actuaciones realizadas en la atención ambulatoria en Salud Mental. Este estudio, es el resultado del registo diagnóstico en las consultas ambulatorias en Centros de Salud Mental de la Comunidad de Madrid a lo largo de 30 años y con más de 8 millones de registros de consultas en general. En relación al trastorno bipolar se han recogido 884.999 registros de consultas a lo largo del tiempo para 21.674 pacientes con al menos un diagnóstico bipolar. Este amplio y prolongado registro ha posibilitado, hasta el momento, la realización de múltiples trabajos de investigación epidemiológica y estabilidad diagnóstica en trastorno mentales (Baca-Garcia et al. 2007; Baca-Garcia et al. 2007[2]; Baca-Garcia et al. 2008; Basurte et al. 2006). Así, el grupo de trabajo se ha centrado anteriormente en el estudio de la estabilidad diagnóstica del trastorno bipolar (Baca-Garcia et al. 2007[2]; Lopez-Castroman et al. 2008; Garcia-Castillo et al. 2012) en algunos distritos sanitarios de Madrid; y estos estudios ya tenían un tamaño muestral mayor que otros foráneos. En el presente trabajo se ha ampliado el área de estudio a toda la Comunidad de Madrid, con lo que se obtenido una muestra que duodecuplica la anterior (Baca-Garcia et al. 2007[2]).

El objetivo de este trabajo es realizar un estudio ecológico sobre la estabilidad del trastorno bipolar en seguimento en los Centros de Salud Mental de la Comunidad de Madrid entre los años 1980 y 2009. El trastorno bipolar es una enfermedad con una prevalencia significativa en la población general y es necesario que su diagnóstco se realice de forma precoz para que su evolución presente un buen pronóstico. La estabilidad diagnóstica para el trastorno bipolar a lo largo de su evolución va a determinar un planteamiento terapéutico adecuado desde las fases tempranas de la enfermedad. Por tanto, un estudio ecológico, en ámbitos sanitarios y de práctica clínica habituales, de la estabilidad y la evolución a largo plazo del diagnóstico de trastorno bipolar se considera de interés y puede aportar nuevas evidencias sobre este tema.

3 ANTECEDENTES Y RELEVANCIA

Resumen

La importancia de la evaluación longitudinal se ha destacado a menudo para determinar la validez de los diagnósticos en psiquiatría. La estabilidad refleja la concordancia de los diagnósticos a lo largo del tiempo y puede determinarse a través de diferentes instrumentos. El trastorno bipolar genera una carga importante y, sin embargo, existe una alta prevalencia de diagnósticos erróneos que pueden contribuir en gran medida a aumentar los costes. En resumen, un número comparativamente pequeño de estudios han sido diseñados intencionadamente para revisar la relevancia de la estabilidad diagnóstica, tanto en el caso particular del trastorno bipolar como aplicada a las condiciones psiquiátricas generales. Los resultados de los estudios epidemiológicos existentes sobre el trastorno bipolar han mostrado una consistencia de moderada a alta en el diagnóstico de trastorno bipolar. Si bien estos estudios anteriores han proporcionado información detallada sobre la estabilidad diagnóstica de los trastornos bipolares, en términos generales están limitados por unos pocos puntos de evaluación y un breve seguimiento. Además, el uso de intervalos de tiempo fijos predeterminados entre los puntos de evaluación puede haber contribuido a la aparición de sesgos de recuerdo. Dada la escasez de información sobre la estabilidad diagnóstica de los trastornos bipolares, se intentó evaluar su estabilidad a largo plazo en una gran muestra de población adulta que fue evaluada en múltiples puntos temporales, al menos diez durante al menos un año, en un contexto clínico de práctica habitual. Este estudio proporcionó una oportunidad única para arrojar luz sobre la cuestión de la estabilidad de los diagnósticos del trastorno bipolar a lo largo del tiempo y de cómo el grado de estabilidad diagnóstica puede influir en la práctica clínica, determinando así la carga de esta enfermedad. Se planteó la hipótesis de que la estabilidad en el tiempo de los trastornos bipolares podría diferir cuando se evalúan en múltiples puntos y durante un período de tiempo más largo, en comparación con los estudios anteriores.

La utilización de un “gold standard” en los procedimientos diagnósticos es particularmente problemática en psiquiatría, donde el diagnóstico de una patología se determina principalmente por sus manifestaciones clínicas, más que por sus marcadores biológicos (Sanjuán 2001). Así, los límites categoriales de las entidades nosológicas son habitualmente difusos en psiquiatría (Zachar et Kendler 2007) y el solapamiento diagnóstico no es infrecuente. Los estudios genéticos han elevado las expectativas de una mayor compresión de estas categorías diagnósticas, sin embargo, es dudosa la repercusión de estos hallazgos en una redefinición nosológica (Sanjuán 2001; Kendler 2006). De hecho, un estudio muestra la evidencia de un gran número de genes implicados en la aparición de la enfermedad (Segurado et al. 2003). Krishnan, en 2005, describe los siguientes criterios para definir una enfermedad:

- Debe unificar el riesgo de evolución adversa, desajuste funcional y mortalidad.
- Si una característica identificable (factor ambiental, patología o factores genéticos) puede ser definida con claridad debería separar la entidad de otras similares en al menos uno de los siguiente criterios:
    1. síntomas clínicos,
    2. curso y evolución,
    3. patrón familiar y,
    4. respuesta al tratamiento.
- Si una característica no identificable puede ser definida con claridad, llamado hecho nominalístico, debería separar la entidad de otras similares en al menos uno de los siguiente criterios:

1. curso y evolución,
2. patrón familiar y,
3. respuesta al tratamiento.

Lo más extendido es considerar a la patología bipolar como un trastorno (WHO 1992). Según Pies, un trastorno debe cumplir uno de los siguientes criterios para ser considerado una "entidad de enfermedad específica" (Pies 2009):

- Un patrón de transmisión genética.
- La etiología, fisiopatología y / o anatomía patológica del síndrome debe ser razonablemente conocida.
- El curso, el pronóstico, la estabilidad y la respuesta al tratamiento del síndrome deben ser relativamente predecibles y consistentes en diferentes poblaciones.

También se ha apuntado a las características psicológicas individuales (Ovejero et a. 2014) como un factor a tener en cuenta para configurar un trastorno.

Así, la estabilidad del trastorno hace posible que se pueda identificar al mismo como una entidad nosológica y, de la misma forma, esta estabilidad se hace extensible a una necesaria estabilidad diagnóstica para un determinado trastorno.

Mientras las lesiones tisulares que aparecen en los exámenes patológicos son empleados como “gold standard” para establecer la presencia de un trastorno determinado en la mayoría de campos médicos (Boutros et al. 2005), en psiquiatría deben ser usados diferentes instrumentos para garantizar la consistencia de un diagnóstico:

- El Mejor Diagnóstico Estimado: considerado el método más válido para

diagnosticar trastornos en psiquiatría (Boutros et al. 2005; Leckman et al. 1982; Kosten et Rounsaville 1992; Roy et al. 1997), está basado en el acuerdo entre un número de expertos; es un diagnóstico basado en la entrevista personal, la historia familiar y los antecedentes médicos. Dos estudios muestran que los diagnósticos basados en datos clínicos, usando una evaluación multimodal para llegar a un consenso diagnóstico, presentan un estadístico kappa de acuerdo de un 0.69 (Leckman et al. 1982; Roy et al. 1997).

- La evaluación longitudinal llevada a cabo por un experto, usando todos los datos disponibles, fue concebida como un estandar para la validación de diagnósticos psiquiátricos (procedimiento LEAD ["longitudinal, expert, all data"]) (Torrens et al. 2004; Spitzer 1983).

También se ha resaltado la importancia de la evaluación longitudinal y el uso de múltiples fuentes de información como medios diagnósticos (Perala et al. 2007). Este estudio demuestra que la prevalencia-vida de trastornos psicóticos puede estar subestimada en la población general utilizando el Mejor Diagnóstico Estimado. En el actual estudio se pretende seguir una vía similar para mostrar la importancia del diagnóstico longitudinal y su estabilidad en el trastorno bipolar.

3.1 CONCEPTO DE ESTABILIDAD

La estabilidad diagnóstica es la medida del grado en que el diagnóstico permanence igual en las subsecuentes valoraciones de un paciente, y constituye una validación longitudinal del diagnóstico basal. Está basado en la concordancia del diagnostico a lo largo del tiempo y no tiene en cuenta el diagnóstico transversal en un punto concreto del seguimiento (Fennig 1994). Tradicionalmente, la evolución y el pronóstico de los trastornos psiquiátricos han jugado un importante papel en los criterios diagnósticos desde inicios de siglo XIX. Kahlbaum diferenció entre demencia aguda y crónica y Kraepelin consideró que la evolución y respuesta de los trastornos era esencial para el diagnóstico (Gelder et al. 2003; Vallejo et Leal 2005). Los estudios de seguimiento que presentan evidencias de estabilidad y consistencia diagnósticas a lo largo del tiempo han sido propuestos como test de validez de los diagnósticos psiquiátricos (Burger y Neeleman 2007):

- Robins y Guze en 1970 realizaron una lista de cinco criterios para la validez de los diagnósticos psiquiátricos: 1) descricción clinica, 2) estudios de laboratorio, 3) delimitación de otros trastornos, 4) estudios de seguimiento incluyendo evidencias de estabilidad diagnóstica, y 5) estudios familiares. En su artículo, proponen por primera vez la relación entre estabilidad diagnóstica y validez predictiva.
- Kendler en 1980 revisó este esquema, distinguiendo entre 1) criterios antecedentes de validez, 2) criterios concurrentes de validez, 3) criterios predictivos de validez que incluyen la consistencia diagnóstica a lo largo del tiempo, tasas de recaída, de remisión y de respuesta al tratamiento.
- Andreasen en 1995 propuso resumir los métodos de validación más novedosos que vinculen síntomas y diagnósticos a sus sustratos neuronales, con una aproximación clínica y epidemiológica que incluya criterios de validez, tales como el curso característico de la enfermedad y los estudios de seguimiento para determinar la evolución.
- First et al. en 2004 definió la validez diagnóstica como un complejo constructo multifactorial que incluye un número de diferentes tipos de validez: 1) Validez aparente, significando el hecho de describir pormenorizadamente el trastorno; 2) Validez descriptiva, si los hechos de una categoría sirven para diferenciala de otras; 3) Validez predictiva, el grado con el que un diagnóstico predice el curso clínico futuro o la estabilidad diagnóstica; 4) Validez externa, asociada con los criterios de validez externa esperados. Esta nueva definición logró enmendar la debilidad de los criterios de validez anteriores, que implícitamente suponían que los trastornos psiquiátricos eran entidades discretas (Kendell et Jablensky 2003).

En el actual trabajo se presentan los conceptos de estabilidad diágnostica prospectiva y estabilidad diágnostica retrospectiva. Estos conceptos se equiparan con los de consistencia prospectiva y retrospectiva. La consistencia prospectiva (conceptualmente similar al valor predictivo positivo) es la proporción de sujetos en una categoría de diagnóstico en la primera evaluación que recibieron el mismo diagnóstico en su última evaluación. La consistencia retrospectiva (conceptualmente similar a la sensibilidad) es la

proporción de sujetos en una categoría de diagnóstico en la última evaluación que estaban en esa misma categoría al inicio del estudio (Mojtabai et al. 2003; Grilo et al. 2004; McGlasham et al. 2005).

3.2 IMPORTANCIA DE LA ESTABILIDAD DIAGNÓSTICA

Hasta este momento las definiciones de los diagnósticos psiquiátricos están basadas en la opnión experta más que en sus bases biológicas, y el modesto conocimiento de las etiologías subyacentes ha limitado el papel de estos factores etiológicos en los sistemas de clasificación (Baca-Garcia et al 2007; Lopez-Castroman 2011). La estabilidad diagnóstica da una base firme no solo para la predicción del curso y repuesta de un trastorno, sino también para una efectiva planificación y prestación del tratamiento (Mezzich et Berganza 2005).

La introducción de criterios diagnósticos explícitos en varios sistemas de clasificación , como el DSM-III o la CIE-10, ha afectado profundamente la práctica psiquiátrica (Helmuth 2003). Esta estructura de referencia estandarizada ha permitido conseguir mejores acuerdos diagnósticos y mejorar la información y análisis estadísticos (Kendler 2003). Las clasificaciones han contribuido progresivamente a un mayor reconocimiento y diagnóstico de los trastornos psiquiátricos. La disponibilidad de datos longitudinales puede causar, sin embargo, fluctuaciones significativas tanto en la estabilidad diagnóstica como en los cambios en la presentación clínica (Krishnan 2005). Por tanto, el desarrollo de observaciones longitudinales debería actualizar las formulaciones diagnósticas comprensivas (IGDA 2003), a pesar de los problemas inherentes a los criterios basados en observaciones transversales (Kendler 1985).

3.2.1 Estabilidad estimada

La estabilidad diagnóstica ha entrado en funcionamiento en diferentes formas según los revisores (Fennig et al. 1994). La mayoría de estudios logitudunales usstilizan datos basados en el curso de la enfermedad y en los patrones de síntomas a lo largo del tiempo para confirmar o desestimar el diagnóstico original. En nuestro estudio usaremos la aproximación más común, examinando la estabilidad del trastorno bipolar a la luz de de multiples evaluaciones a lo largo de la evolución de la enfermedad. Solo un estudio anteriormente ha considerado un diagnóstico como estable solo si la confirmación de criterios era estable a lo largo del seguimiento (Beiser et al. 2007). Este único estudio, que menciona la estabilidad temporal a corto plazo de los trastornos psicóticos en una muestra al ingreso, encuentra que el 80% de los pacientes inicialmente clasificados como trastorno bipolar y trastorno depresivo mayor, no tenían síntomas y no recibían diagnóstico a los 9 y 18 meses respectivamente.

La tasa de concordancia positiva describe el porcentaje de aquellos diagnósticos de un trastorno que se mantiene igual en la primera valoración y las siguientes (presente-presente). Sin embargo, hay una deficiencia en este parámetro: falla para explicar la introducción de nuevos casos de un trastorno. El coeficiente kappa es capaz de corregir este problema para explicar las tasas de concordancia positiva y negativa, así como las tasas de casos discordantes (Bartko 1991; Langenbucher et al. 1996). En este sentido, el coeficiente kappa proporciona una estimación más comprensiva de la estabilidad y corrige el acuerdo debido a la casualidad; así, es comúnmente preferido a las tasas de concordancia. A pesar de todo, el coeficiente kappa puede producir un error para estimar la estabilidad si se presenta solo; se reduce groseramente con altas incidencias de nuevos casos y magnifica excesivamente con altas tasas de concordancia negativa. Teniendo en cuenta estos peligros, es importante examinar ambos, tasas de concordancia y coeficiente kappa, para establecer la estabilidad diagnóstica con exactitud (Altman et al. 2000).

3.3 LOS ANTECEDENTES DEL TRASTORNO BIPOLAR

El trastorno afectivo bipolar es un trastorno mental clasificado en la CIE-10 (WHO 1992). Es un trastorno caracterizado por la presencia de episodios reiterados (es decir, al menos dos) en los que el estado de ánimo y los niveles de actividad del enfermo están profundamente alterados, de forma que en ocasiones la alteración consiste en una exaltación del estado de ánimo y un aumento de la vitalidad y del nivel de actividad (manía o hipomanía) y en otras, en una disminución del estado de ánimo y un descenso de la vitalidad y de la actividad (depresión). Lo característico es que se produzca una recuperación completa entre los episodios aislados. A diferencia de otros trastornos del humor (afectivos), la incidencia en ambos géneros es aproximadamente la misma.

3.3.1 Epidemiología

La tasa de prevalencia, largamente debatida, se acepta actualmente que se encuentra entre el 1-2% de la población general, aunque el espectro bipolar no se incluye en esta estimación (Sajatovic 2005). Los hallazgos presentados el estudio europeo multicéntrico ESEMed revelan frecuencias menores, por debajo del 1% (ESEMed

2004; Alonso et al. 2004). El estudio NEMESIS sugiere una prevalencia para el trastorno bipolar de 1,9% (Bijl et al. 1998). El estudio ECA (Epidemiologic Catchment Area) encuentra una prevalencia a lo largo de la vida de 1,3% (0.8% para el tipo I y 0,5% para el tipo II) (Bebbington et Ramana 1995). El estudio NCS (National Comorbidity Survey) coloca la prevalencia a lo largo de la vida para la manía y la hipomanía en un 1,6% (Kessler et al. 2005). En España, dos autores han estudiado la prevalencia del trastorno bipolar en muestras pequeñas; Vázquez-Barquero et al. encuentran una tasa del 0,08% para la psicosis maniacodepresiva de tipo maníaco, y Canals et al. encuentran una prevalencia del 2,4% para la hipomanía (CIE-10) (Vazquez-Barquero et al. 1986 y 1987; Canals et al. 1997). La alta variabilidad en los resultados, del 0,2 al 3,3%, se observa cuando se incluyen estudios llevados a cabo en muestras clínicas pequeñas (Ghaemi et al. 1999; Pini et al. 2005). Esta variabilidad ha sido explicada en relación a differencias metodológicas, comparando el uso de entrevistas estructuradas en encuestas poblacionales con el uso de otros instrumentos (Cegla-Schvartzman et al. 2019; Carta et Angst 2007; Perala et al. 2007; Waraich et al. 2004). Son esenciales múltiples fuentes de información para una adecuada estimación de la prevalencia del trastorno bipolar a lo largo de la vida (Perala et al. 2007).

En las últimas décadas se ha visto una ampliación del concepto del trastorno bipolar y un incremento significativo de su importancia (Jefferson 2006). Es ampliamente admitido que el trastorno bipolar tipo II, el trastorno ciclotímico y otras formas de trastorno bipolar podrían llegar hasta un 5% de la población general (Pini et al 2005; Akiskal et al. 2000; Berk at Dodd 2006; Angst 1995), y por eso se está cambiando del concepto de trastorno al de continuum de enfermedad. Algunos estudios han considerado la posibilidad de un continuo entre la personalidad límite y trastorno bipolar II (Benazzi 2006). En un estudio prospectivo sobre la naturaleza hereditaria de la esquizofrenia y del trastorno bipolar (el estudio Iowa), la prevalencia de mania entre los pacientes con trastorno bipolar, calculado en base a entrevistas diagnósticas, era del 1,9%; sin embargo, cuando se consideran fuentes adicionales de información, tales como datos clínicos y entrevistas con familiares, la tasa aumenta hasta un 5,3% (Tsuang et al. 1980). Un estudio comunitario longitudinal de veinte años llevado a cabo en Zurich (Angst et al. 2003) encuentra que los pacientes depresivos con un síndrome subumbral de hipomanía era similar al trastorno bipolar II en términos de historia familiar para manía, curso, tasas de comorbilidad y de tratamiento. Así, los síntomas maníacos subumbrales en la adolescencia han sido descritos como altamente predictivos de un subsecuente inicio de un episodio maníaco (Lewinsohn et al. 1999; Lewinsohn et Seeley 2003).

3.3.2 Error diagnóstico

El inicio del trastorno bipolar es frecuentemente traicionero, presentando un cuadro confuso a nivel clínico (Berk et al. 2006). Muchos pacientes experimentan alteraciones de la esfera emocional antes del primer episodio de enfermedad, mientras otros pacientes presentan episodios mayores de enfermedad sin un claro pródromo. Se han descrito algunas presentaciones de la depresión bipolar para distinguirla de la depresión unipolar: síntomas atípicos, inicio y fin abrupto, patrón de alta recurrencia, historia familiar, inicio de enfermedad a edad temprana (Thase 2006). Sin embargo, los actuales sistemas de clasificación usan el mismo conjunto de síntomas para describir ambos tipos de depresión. La alta proporción de error diagnóstico en las primeras consultas se puede explicar porque la búsqueda de ayuda por parte del paciente bipolar suele ser la presencia de sintomatología depresiva, no tanto así por la clínica maniforme (García-Castillo et al. 2012). El estigma y la incomprensión de la enfermedad también podría explicar el retraso diagnóstico. También merece la pena señalar que los episodios depresivos son la causa más común de morbilidad e, incluso, de fallecimiento por suicidio (Emilien et al. 2007).

La problemática diagnóstica del trastorno bipolar ha sido expuesta en varios estudios. De acuerdo a los dartos recogidos de la NDMDA (the National Depressive and Manic-Depressive Association), la prevalencia de error diagnóstico en la valoración inicial de pacientes bipolares tiene una rango del 48% (Lish et al. 1994) al 69% (Hirschfeld et al. 2003), la mayoría se confunde con depresión unipolar. Los datos de 2000 NDMDA muestran que el 31% de pacientes bipolares han sido mal diagnosticados como depresión unipolar y, cerca de la mitad (49%), esta condición nunca fue reconocida ni diagnosticada (Hirschfeld et al. 2003; Berk et al. 2006). Ghaemi et al. 1999, presentan evidencias de un infradiagnóstico de trastorno bipolar en muestras clínicas: el 40% de los pacientes han recibido un diagnóstico erróneo de depresión mayor. Resultados similares han sido publicados por Angst et al. en 2002, del 25 al 50% de los casos de depresión mayor al inicio en su muestra estaban actualmente afectos de trastorno bipolar. Hirschfeld et al, 2003, comunicaron un tiempo medio para el diagnóstico de trastorno bipolar de más de 10 años en la tercera parte de la muestra, y que los que habían sido mal diagnosticados habían consultado una media de cuatro médicos antes de

recibir el diagnóstico correcto. Un estudio sobre el tiempo medio desde el inicio de la enfermedad al tratamiento de mantenimiento con litio, muestra una media de 8,38 años en una muestra de pacientes bipolares (Baldessarini et al. 1999). La media de vacío terapéutico, la proporción de individuos con un trastorno psiquiátrico que se mantienen sin tratamiento a pesar de existir un tratamiento efectivo, se ha calculado que es del 50,2% en la población mundial para el trastorno bipolar (Kohn et al. 2004).

El error diagnóstico complica los intentos de un manejo efectivo del trastorno bipolar y también juega un papel importante en la carga económica de la enfermedad (Hirscgfeld et al. 2003). Las evidencias emergentes sugieren que una intervención temprana influye en una respuesta más favorable del trastorno bipolar; de la misma manera, un retraso en el incio del tratamiento con estabilizadores del ánimo se ha asociado con un incremento de los costes sanitarios (Li et al. 2002). Unos diagnósticos y tratamientos acertados pueden proteger contra el deterioro functional asociado con el trastorno bipolar (Fagiolini et al. 2005).

3.3.3 La carga del trastorno bipolar

De acuerdo con el informe de 2001 de la Organización Mundial de la Salud, el trastorno bipolar es la quinta causa de discapacidad a nivel mundial en el grupo de edad de 15 a 44 años, y la novena en todas las edades (WHO 2001). Es la séptima causa mundial de carga de enfermedad no letal. Se estima que el coste del trastorno bipolar, durante 2002 en el Reino Unido, en 2.000 millones de libras (Pini et al. 2005); en 1991 se estima el coste total anual de aproximadamente 2 millones de casos prevalentes en Estados Unidos en 45.000 millones de dólares (Wyatt et Henter 1995). En 2013 se clasificó al trastorno bipolar como la 16ª causa principal de años vividos con discapacidad (Ferrari et al. 2013). El tratamiento con litio a nivel ambulatorio y la atención psicosocial fueron las intervenciones mejor coste-eficacia para reducir la carga de esta enfermedad (Chisholm et al. 2005). En estos estudios no se incluía el espectro bipolar.

Siguiendo la terminología más frecuente en los estudios de costes de enfermedad, los costes directos incluyen todos aquellos producidos directamentes por la atención médica, mientras que los costes indirectos derivan del nivel de incapacidad, el efecto en la productividad laboral, efectos en la asistencia social y los costes relacionados con los procesos judiciales (Chisholm et al. 2005). Los costes directos sanitarios derivados de la enfermedad eran significativamente superiores en pacientes que no estaban diagnosticados inicialmente de trastorno bipolar, los cuales no reciben tratamiento con estabilizadores del ánimo después de un primer episodio afectivo según el California Medicaid Program (Li et al. 2002). A pesar de todo, la mayoría del coste del trastorno bipolar deriva de los costes indirectos relacionados con la disminución de la capacidad functional y la pérdida del trabajo (Hirschfeld et al. 2005). El trastorno bipolar está asociado con altas tasas de desempleo, dificultades laborales y estrés interpersonal (Sajatovic 2005). En una encuesta, el 88% de los participantes referían dificutades laborales (Hirschfeld et al. 2003).

En un estudio de una cohorte nacional danesa (Hakulinen et al. 2019) las tasas de población de trastorno bipolar diagnosticada en el hospital entre las edades de 15-25 fueron del 1%. En comparación con las personas sin trastornos del estado de ánimo, las personas con trastorno bipolar tuvieron resultados socioeconómicos consistentemente pobres en toda la vida laboral. Por ejemplo, a los 30 años, el 62% de los casos bipolares estaban fuera de la masa laboral en comparación con el 19% de la población general, y el 52% de los casos bipolares no tenían educación superior en comparación con el 27% de la población general.

En un estudio de 2014, encuentran unos hallazgos que respaldan el predominio de los síntomas depresivos en comparación con la elevación del estado de ánimo y/o síntomas mixtos en el curso de la enfermedad bipolar y, por lo tanto, una mayor carga general en términos de costes económicos, funcionamiento, carga del cuidador y suicidio (Miller et al. 2014).

El tratamiento del trastorno bipolar podría mejorar si los servicios públicos de salud promocionasen el diagnóstico y el tratamiento precoces (Lish et al. 1994). En un estudio basado en ESEMeD, Fernández et al. en 2006 encontraron que sólo un tercio de los tratamientos de salud mental en España reunen mínimamente criterios adecuados. La Organización Mundial de la Salud (WHO, en sus siglas en inglés), a través del programa "CHOosing Interventions that are Cost-Effective (WHO–CHOICE), revelan que, asumiendo un 50% de covertura poblacional, las intervenciones clínicas pueden reducir potencialmente la carga del trastorno bipolar entre un 10 y un 33 % (Chisholm et al. 2005).

3.3.4 Comorbilidad

En el trastorno bipolar concurre un conjunto de patrones de enfermedad, incluidos la ciclación rápida, los estados mixtos y una extensa comorbilidad que suelen complicar el diagnóstico

y el tratamiento y contribuyen al coste de la enfermedad (Hirschfeld et al. 2005; McElroy 2004). Las tasas de comorbilidad se han estimado sobre el 50% en algunos estudios (Strakowski et al. 1992; Kessler et al. 1994; Cassano et al. 1998; Black et al. 1988; McElroy et al. 2001). Vieta et al. presentan una tasa de comorbilidad del 31%, en una muestra de pacientes bipolares españoles en 2001. Esta diferencia, según explica el autor, es debida a la selección de pacientes eutímicos en servicios ambulatorios psiquiátricos primarios, lo que evita el riesgo de confundir sintomatología afectiva aguda con aquella secundaria a otra enfermedad.

Entre la comorbilidad más frecuente del trastorno bipolar se incluye:

- Abuso de sustancias y alcohol. Se estima el abuso comórbido de drogas en un rango entre el 14 y el 60%, según la revisión realizada por Cassidy et al. en 2001; la mayoría de autores lo sitúa por encima del 30%. McElroy et al. en 2001 describen un 42% de uso prejudicial de sustancias comórbido en una muestra de 288 pacientes. En el estudio ECA, los pacientes bipolares tipo I presentaban más de tres veces de abuso o dependencia de alcohol y unas siete veces más de abuso o dependencia de sustancias que la población general (Reiger et al. 1990).
- Trastornos de ansiedad. Se han encontrado altas tasas de comorbilidad a lo largo de la vida con trastorno de pánico (21%) y trastorno obsesivo compulsivo (21%) para pacientes bipolares tipo I y II incluidos en la encuesta ECA (Chen et Dilsaver 1995). McElroy et al. encontraron un 42% de comorbilidad con trastornos de ansiedad (McElroy et al. 2001). En el estudio NCS, el 92% de los pacientes bipolares tipo I también presentan criterios a lo largo de su vida para trastorno de ansiedad (Kessler et al. 1994).
- Trastornos de personalidad. Cuando se evalúa a pacientes bipolares en periodos eutímicos, las tasas de comorbilidad con trastornos de personalidad están alrededor del 30% (George et al. 2003; Vieta et Colom 1999; Barbato et al. 1998; Kay et al. 1999). Los trastornos de personalidad de los cluster B y C son los más comórbidos con el trastorno bipolar (George et al. 2003; Pica et al. 1990; O'Connell et al. 1985). Un trastorno de personalidad predice una peor adherencia al tratamiento entre bipolares adultos (Colom et al. 2000; Schou 1988), y la ausencia de apoyo social predispone a un peor funcionamiento global (O'Connell et al. 1985).
- Trastorno de deficit de atención e hiperactividad (TDAH). La síntomatología del TDAH y el trastorno bipolar se solapan frecuentemente (Dilsaver et al. 2003; Leboyer et al. 2005). Esto puede producer errores en el diagnóstico y, por tanto, en el tratamiento (los psicoestimulantes pueden inducer manía o ciclación rápida). Las tasas de comorbilidad con TDAH están en un rango entre 60% y 90% (Biederman et al. 2000).
- Suicidio. El trastorno bipolar representa un importante factor de riesgo tanto para los intentos de sucidio como para el suicidio consumado (Angst et al. 2003). Las tasas de suicidio, con una media del 0,4% para pacientes bipolares, son veinte veces mayores que en la población general (Tondeo et al. 2003). El trastorno bipolar ha mostrado una fuerte relación entre historia de intentos de suicidio (29,2%), familiares con depresión unipolar (15,9%) y otros trastornos del Eje I (4.2%) (Chen et Dilsaver 1996).

3.4 ESTABILIDAD EN TRASTORNO BIPOLAR

3.4.1 Limitaciones en trastorno bipolar

En el artículo original de Blacker and Tsuang publicado en 1992, el trastorno bipolar era llamado a ser una de las entidades diagnósticas más robustas en psiquiatría, aunque identificaban una serie de limitaciones que cuestionaban si unos criterios diagnósticos mejorados podrían ser necesarios para algunas investigaciones y propuestas clínicas. Entre las razones que podrían demostrar la distintiva fenomenología del trastorno bipolar, se mencionaban las siguientes: su apación a lo largo de la historia (Berrios 1996; Alvarez 1999; Benavent-Rodriguez 2001) y diferentes culturas (Weissman et al. 1996), sus patrones de presentación (Tsuang et al. 1980; Angst 2003), y sus claras alteraciones de la función fisiológica (Goodwin et Jamison 1990).

La heterogenicidad en la expresión y evolución de las manifestaciones clínicas del trastorno bipolar complica sustancialmente un diagnóstico correcto y temprano de esta enfermedad. El diagnóstico de trastorno bipolar, especialmente durante las fases agudas de la enfermedad, está habitualmente dificultado por la inestabilidad de los síntomas, la negación del mismo por parte de pacientes y familiares, inconsistencias en la información recogida retrospectivamente, la presencia concomitante de consumo de drogas o trastornos de la

personalidad, la confusión entre síntomas afectivos y psicóticos y el solapamiento con otras patologías del eje I (Kendell 1985). Algunas patologías que pueden crear confusión en el correcto diagnóstico de trastorno bipolar son:

- Esquizofrenia. La principal causa de un diagnóstico inadecuado de trastorno bipolar es la confusión con esquizofrenia (Palomar-Ciria et al. 2019;Taylor 1992; Tsuang et al. 1981; Tsuang et al. 1980). La clasificación del paciente puede no estar clara cuando presenta una sintomatología similar y que comparten ambas (Marneros et al. 1991). El trastorno esquizoafectivo se ubica en una zona entre ambos diagnósticos e incluye los casos en los que los síntomas psicóticos no están claramente unidos a los episodios afectivos (Blacker et Tsuang 1992).
- Depresión unipolar (Kendler et Gardner 1998). Debido a la alta prevalencia de la depression unipolar, la diferencia con la depression bipolar llega a ser de extremada importancia. El fallo en el reconocimiento de los potenciales bipolares (o falsos unipolares) (Goodwin et Jamison 1990) es una de los principales escollos para determinar correctamente la prevalencia del trastorno bipolar. El trastorno bipolar tipo II juega un papel limitante, ya que muchos investigadores lo identifican, en cuanto a curso de enfermedad y características epidemiológicas, con el tipo I (Angst 1998). Las dificultades en la valoración de la hipomanía limitan la aplicación del diagnostico del tipo II (Rice et al. 1986; Berk et Dodd 2005).
- Trastornos de personalidad. La confusión con trastorno de personalidad se centra principalmente en el de tipo límite (Krishnan 2005). Hay hallazgos contradictorios en cuanto a la relación del trastorno límite de personalidad y el trastorno bipolar (Akiskal 2004; Magill 2004; Rugero et al. 2010). También se ha incluido como parte del espectro bipolar (Angst et al. 2015). El solapamiento sintomático con el trastorno bipolar tipo II ha sido relacionado con la inestabilidad emocional y la impulsividad, ambos criterios diagnósticos del trastorno límite de personalidad (Benazzi 2006).
- El abuso de drogas puede enmascarar síndromes afectivos en consumidores de sustancias y que se diagnostique erróneamente como trastorno bipolar. (Casas 2000). Pueden aparecer tanto falsos positivos, pacientes intoxicados con estimulantes que pueden ser considerados equivocadamente como maníacos (Black et al. 1988), como falsos negativos, debido al enmascaramiento (Blacker et Tsuang 1992).
- Deberían ser considerados los síndomes infantiles, incluidos la manía y la depresión de inicio temprano (Kim-Cohen et al. 2003; Kovacs et al. 1984;1 Lewinsohn et Seeley 2003; Carlson et al. 2002; Costello et al. 2003; Hofstra et al. 2000; Fergusson et al. 1993). Se ha encontrado una asociación entre el inicio a una edad temprana y un incremento en el cambio de trastorno unipolar a bipolar (Harrington et al. 1990). El trastorno de déficit de atención e hiperactividad también se puede confundir con el trastorno bipolar, debido a un sustancial solapamiento de sus sintomatologías (Dilsaver et al. 2003; Cohen et al. 1993; Ramos-Quiroga et al. 2006).
- Ciclotimia. Una ciclación anímica del trastorno bipolar tipo II puede ser difícil de distinguir de la ciclación temperamental de la ciclotimia (Akiskal et al. 2000; Krishnan 2005). Algunos autores proponen la labilidad emocional subumbral de la ciclotimia como el punto de unión con el espectro bipolar (Perugi et Akiskal 2002; Angst et al. 2015).

3.4.2 Literatura sobre la estabilidad del trastorno bipolar

Más alla de las dificultades diagnósticas, la mayoría de los estudios hasta la fecha sugieren unos niveles entre moderados y altos de estabilidad diagnóstica del trastorno bipolar (Fennig et al.1994; Chen et al. 1998; Marneros et al. 1991; Schwartz et al. 2000; Amin et al. 1999; Schimmelmann et al. 2005; Veen et al. 2004; Addington et al. 2006; Tsuang et al. 1981). La mayoría de las investigaciones hasta el momento están limitadas por el uso de pocos puntos de evaluación, dos o tres en la mayoría de ellos, y cortos períodos de seguimiento, lo que genera preocupaciones sobre la generalización de los resultados y sugiere la necesidad de desarrollar nuevos estudios capaces de superar tales limitaciones. Como las evaluaciones generalmente se llevan a cabo en dos puntos remotos en el tiempo, en la mayoría existe un intervalo de tiempo entre ellas que no se controla para el estado del diagnóstico y los cambios temporales del mismo. Por otro lado, la mayoría de los estudios previos no analizaron los factores relacionados con el cambio diagnóstico ni informaron los diagnósticos posteriores de

pacientes que no recibieron un diagnóstico específico al ingresar al estudio.

A continuación se describen brevemente los estudios epidemiológicos y clínicos que han evaluado la estabilidad diagnóstica del trastorno bipolar utilizando las consistencias temporales y/o las estimaciones de kappa. Los siguientes estudios se centran exclusivamente en la estabilidad del diagnóstico del trastorno bipolar:

1. Weeke et al. publicaron en 1984 un estudio basado en el Danish Psychiatric Register. Esta base de datos contiene información sobre los pacientes ingresados en instituciones psiquiátricas danesas. Estudió la evolución de los pacientes que habían sido admitidos entre abril de 1970 y marzo de 1972 por primera vez, y que tenían al menos un ingreso más antes de marzo de 1977, que se clasificaron como maniáco-depresivos con criterios de la CIE-8 en cualquiera de los ingresos. 3.062 personas cumplieron los criterios. Después del período de observación, 623 personas (20% de la muestra de registro) fueron clasificadas retrospectivamente como bipolares. Sin embargo, en su estudio, los diagnósticos maníaco-depresivos incluyeron pacientes unipolares y bipolares y sus resultados con respecto a la estabilidad del diagnóstico maníaco-depresivo se vuelven engañosos, siendo el principal hallazgo del estudio que el diagnóstico maníaco-depresivo es más estable entre los pacientes bipolares que entre los unipolares. En este estudio se puede calcular una estabilidad diagnóstica retrospectiva del 20% (IC 95%: 18.6 - 21.4).

2. Chen et al. revisaron en 1998 los registros de 936 pacientes con al menos 4 hospitalizaciones dentro de los 7 años para evaluar el cambio diagnóstico del trastorno bipolar a otros trastornos mentales. La base de datos del hospital contenía información longitudinal sobre los diagnósticos de estos pacientes, asignados siguiendo los criterios del DSM-III-R. El conjunto de pacientes se dividió en dos grupos con respecto al diagnóstico inicial de trastorno bipolar o cualquier otro trastorno mental para estudiar el flujo de diagnóstico. Se utilizó un subconjunto de 443 pacientes con diagnósticos iniciales y posteriores de trastorno bipolar y/o esquizofrenia para estudiar específicamente el flujo entre trastorno bipolar y esquizofrenia. Para comparar las tasas de cambios de diagnóstico hacia y desde trastorno bipolar se utilizaron chi-cuadrado o las pruebas exactas de Fisher. Los resultados mostraron que solo el 60% de los sujetos que completaron el período de estudio con un diagnóstico de trastorno bipolar comenzaron el estudio con el mismo diagnóstico. Se encontró que el cambio de diagnóstico más frecuente de trastorno bipolar fue a esquizofrenia (70.1%), aunque solo el 24.8% de aquellos que cambiaron a trastorno bipolar cambiaron de esquizofrenia. El estudio también encontró que más mujeres que hombres cambiaron el diagnóstico a trastorno bipolar y que los afroamericanos tenían más probabilidades de cambiar de trastorno bipolar a esquizofrenia. Como se evaluó la estabilidad en las poblaciones de readmisión hospitalaria, la fiabilidad de estos diagnósticos clínicos está limitada por el sesgo inherente en el muestreo de pacientes rehospitalizados (16). En este estudio se puede calcular una estabilidad diagnóstica prospectiva del 70% (IC 95%: 69.9 - 72.9).

3. Kessing en 2005 investigó la estabilidad diagnóstica del diagnóstico CIE-10 de manía/trastorno bipolar en una muestra de 4.116 pacientes. Los datos se obtuvieron del Danish Psychiatric Central Research Register, una base de datos nacional que incluyó el registro de todas las hospitalizaciones psiquiátricas (1994-2002) e información sobre pacientes en ambulatorios psiquiátricos públicos y centros comunitarios de psiquiatría (1995-2002). Los sujetos habían recibido al menos un diagnóstico de episodio maníaco (F30) o trastorno bipolar (F31) a lo largo del estudio. El seguimiento se dividió en 10 períodos de contacto. La prueba de Chi-cuadrado y la prueba de Mann-Whitney para dos grupos independientes se utilizaron para el análisis estadístico. El 85,4% de las personas con diagnóstico inicial principal de manía/trastorno bipolar (N = 2.315) obtuvieron el diagnóstico de trastorno bipolar al final del segundo período de contacto, y esta proporción disminuyó continuamente hasta el décimo período de contacto (68,8%). Por el contrario, el número de sujetos dentro de este grupo con diagnóstico principal de esquizofrenia aumentó del 4,1% en el segundo período al 12,9% en el último, y el abuso de sustancias del 1,7% al 7,5%. El diagnóstico inicial diferente de manía/trastorno bipolar fue más comúnmente en el espectro afectivo (40.7%), trastornos psicóticos agudos y transitorios (15.6%), trastorno de adaptación (10.4%) o abuso de sustancias (9.2%). Los resultados mostraron que solo el 56.2% de los sujetos obtuvieron el diagnóstico de trastorno bipolar o manía en el primer contacto y que aproximadamente el 30% de los que fueron diagnosticados inicialmente eventualmente cambiaron su diagnóstico durante el seguimiento. La estabilidad del trastorno bipolar se estudió sobre la base de la evaluación inicial. El estudio también encontró que las mujeres y los pacientes más jóvenes tenían un mayor riesgo de retraso en el diagnóstico del trastorno bipolar. En este estudio se puede calcular una estabilidad diagnóstica prospectiva del 68.8% (IC 95%: 67.1 - 70.7).

4. Baca-Garcia et al. publicaron en 2007 la estabilidad diagnóstica a largo plazo del trastorno bipolar con criterios CIE-10 en múltiples entornos terapéuticos. 34.368 pacientes españoles fueron seguidos durante 12 años. Los pacientes tenían 18 años de edad o más y habían recibido al menos una vez un diagnóstico de trastorno bipolar en una de al menos 10 visitas diferentes (n = 1153; 71.543 evaluaciones). El 30% de los pacientes recibió un diagnóstico de trastorno bipolar en la primera evaluación y el 38% en la última evaluación. El 23% de los pacientes recibió un diagnóstico de trastorno bipolar en al menos tres de cada cuatro evaluaciones. Los autores informaron una alta prevalencia de diagnósticos erróneos y cambios diagnósticos de otros trastornos psiquiátricos al trastorno bipolar. La consistencia prospectiva fue del 49% (IC 95%: 46.1 - 51.9) y la retrospectiva del 38% (IC 95%: 35.1 - 40.8).

5. Ruggero et al. presentaron en 2010 un estudio prospectivo de 10 años de seguimiento de 195 pacientes con una primera admisión hospitalaria por psicosis y al menos un diagnóstico de trastorno bipolar en 4 evaluaciones, utilizando criterios DSM-IV. Se realizó un diagnóstico de consenso. Se encontraron unas altas consistencias prospectiva 79.6% (IC 95%: 72.1 - 87.2) y retrospectiva 74.8% (IC 95%: 66.8 - 82.7).

6. Ratheesh et al. publicaron en 2015 un estudio prospectivo de un año de seguimiento de 52 pacientes con patologías mentales prevalentes (depresión, ansiedad y trastorno por uso de sustancias) con criterios de "bipolar en riesgo" (15-25 años de edad, síntomas maníacos por debajo del umbral, depresión por debajo del umbral en combinación con características ciclotímicas o antecedentes familiares de trastorno bipolar). Con criterios DSM-IV observaron un cambio de diagnóstico a trastorno bipolar del 7,7% (IC 95%: 0.4 - 14.9). El pequeño número de conversiones a trastorno bipolar durante el corto período de tiempo de seguimiento limitó el poder del estudio para identificar asociaciones con factores de riesgo que previamente se habían reportado como potenciales para predecir un futuro trastorno bipolar. Sin embargo, los síntomas afectivos por debajo del umbral pueden predecir la aparición de trastorno bipolar entre los jóvenes con trastornos de alta prevalencia.

AUTORES AÑO	N PAÍS	DISEÑO ESTUDIO TIEMPO SEGUIMIENTO	CRITERIOS DE INCLUSIÓN	CRITERIOS DIAGNÓSTICOS	RESULTADOS (IC 95%)
ESTUDIOS CENTRADOS EN TRASTORNO BIPOLAR					
Weeke et al. 1984	3062 Dinamarca	Retrospectivo 7 años	- Al menos un diagnóstico maníaco-depresivo en el momento del ingreso - Reevaluado en segundo ingreso	CIE-8	CR 20% (18.6 - 21.4)
Chen et al. 1998	936 USA	Prospectivo 7 años	- Al menos 4 ingresos - Diagnóstico inicial y final esquizofrenia o TB	DSM-III-R	CP 70% (69.9 - 72.9) CR 60% (56.9 - 63.1)
Kessing et al. 2005	4116 Dinamarca	Retrospectivo 9 años	- Episodio maníaco o TB - 10 periodos de contacto para la evaluación	CIE-10	CP 68.8% (67.1 - 70.7)
Baca-Garcia et al. 2007	1153 España	Prospectivo 12 años	- Un diagnóstico de TB en al menos 10 evaluaciones - Múltiples entornos	CIE-10	CP 49% (46.1 - 51.9) CR 38% (35.1 - 40.8)
Ruggero et al. 2010	195 USA	Prospectivo 10 años	- Primer ingreso por psicosis - Al menos un diagnóstico de TB en 4 evaluaciones - Diagnóstico de consenso	DSM-IV	CP 79.6% (72.1 - 87.2) CR 74.8% (66.8 - 82.7)
Ratheesh et al. 2015	52 Australia	Prospectivo 1 año	- Cumplir con los criterios de BAR (15-25 años, síntomas de manía y depresión subumbrales en combinación con características ciclotímicas o antecedentes familiares de TB)	DSM-IV	Cambio diagnóstico a TB 7,7% (0.4 - 14.9)

Tabla 1. Estabilidad diagnóstica de estudios centrados en trastorno bipolar

TB: Trastorno Bipolar. **IC:** Intervalo de confianza. **DSM-IV-TR**: Manual Diagnóstico y Estadístico de Trastornos Mentales, texto revisado. **ICIE-10**: Clasificación Internacional de enfermedades 10ª edición. **TDM**: Trastorno Depresivo Mayor. **CP**: Consistencia Prospectiva. **CR**: Consistencia Retrospectiva. **RDC**: Criterios Diagnósticos de investigación.

Otros estudios examinaron la estabilidad del diagnóstico del trastorno bipolar después de un episodio psicótico:

1. Jørgensen et al. 1988, en este estudio basado en registros, muestran que la incidencia de pacientes ingresados por primera vez en un hospital psiquiátrico que fueron diagnosticados, con criterios CIE-8, como psicosis funcionales fue de 55 por cada 100.000 habitantes en Dinamarca en 1984. Durante un período de observación de dos años, la mitad de los pacientes fueron readmitidos y dos quintas partes cambiaron su diagnóstico. Los pacientes jóvenes y con esquizofrenia fueron especialmente susceptibles de rehospitalización. La psicosis reactiva y la paranoia fueron los conceptos diagnósticos más inestables, ya que la mitad de los pacientes se clasificaron de manera diferente en el último reingreso en comparación con el primer ingreso. Con los datos aportados en este estudio se puede calcular una consistencia prospectiva del 72.9% (IC 95%: 68.5 – 77.4).

2. Marneros at al. en 1991 investigaron el cambio de síndrome durante el curso de la enfermedad en 355 pacientes con psicosis funcionales. El tiempo medio de observación fue de 25,2 años. Cada episodio fue diagnosticado de forma transversal como esquizofrénico, melancólico, maníaco, mixto maníaco-depresivo, esquizodepresivo, esquizomaníaco o mixto esquizomaníaco-depresivo. Con respecto a todo el tiempo de observación, 148 pacientes cumplieron los criterios diagnósticos DSM-III de trastornos esquizofrénicos, 106 de trastornos afectivos y 101 de esquizoafectivos. Los pacientes con un episodio inicial esquizofrénico mostraron la mayor estabilidad: el 90% no tenía otro tipo de episodio. La mayoría de los pacientes que sufrieron un episodio inicial melancólico permanecieron melancólicos unipolares o desarrollaron sintomatología maníaca, y solo unos pocos sufrieron episodios esquizoafectivos o esquizofrénicos. Los pacientes con una sintomatología maníaca al principio tenían un curso muy inestable y cambiante. La estabilidad de los pacientes con episodios esquizodepresivos iniciales se encuentra entre la de los pacientes con episodios iniciales melancólicos y la de aquellos con episodios iniciales maníacos. Con los datos aportados en este estudio se puede calcular una consistencia prospectiva del 62% (IC 95%: 29.0 – 96.0).

3. Hollister et al. en 1992 publicaron una muestra de pacientes ingresados cuatro o más veces en el mismo hospital psiquiátrico de cuidados agudos durante un período de 3 años. Este estudio reveló que solo 56 de 162 (34%) de estos pacientes fueron dados de alta con el mismo diagnóstico en cada ingreso. La inestabilidad del diagnóstico se produjo a pesar del hecho de que se conocían diagnósticos anteriores y que solo relativamente pocos diagnósticos contribuyeron a este grado de cronicidad. La esquizofrenia y la manía fueron los diagnósticos más estables con una superposición considerable entre ellos. En este estudio se puede calcular una consistencia prospectiva del 52.2% (IC 95%: 37.7 – 66.6).

4. Fennig et al. presentaron en 1994 un estudio epidemiológico sobre la estabilidad a corto plazo de los trastornos esquizofrénicos y otros trastornos psicóticos. 278 sujetos con un primer ingreso constituyeron la muestra. Se realizó un mejor diagnóstico estimado al inicio del estudio y después de 6 meses utilizando la Entrevista Clínica Estructurada para DSM-III-R. Dos psiquiatras examinaron las razones de los cambios en el diagnóstico. Las psicosis afectivas fueron relativamente estables durante el período de 6 meses, el 86,5% de los pacientes mantuvo la misma categoría de diagnóstico. Este estudio abordó también la causa subyacente del cambio diagnóstico, clasificada en 4 posibilidades diferentes: 1) síntomas durante el intervalo, que explicaron el 43% de los cambios; 2) nueva interpretación de los datos originales, es decir, el proceso de diagnóstico en sí mismo, que explicó hasta el 34,3% de los cambios; 3) nueva información de otras fuentes y 4) del paciente, que juntos fueron responsables del 22.1% de los cambios. Entre los hallazgos del estudio, la estabilidad para el trastorno bipolar con psicosis fue más alta que las tasas reportadas en la literatura previa para sujetos hospitalizados con trastorno bipolar. En este estudio se pueden calcular una consistencia prospectiva del 85.7% (IC 95%: 75.7 –94.7) y una retrospectiva del 81.9% (IC 95%: 71.7 – 90.8).

5. Daradkeh et al. en este estudio publicado en 1997 examinan la estabilidad de los diagnósticos CIE-10 de pacientes ingresados en la unidad psiquiátrica de pacientes hospitalizados de Al Ain (Emiratos Árabes Unidos) durante el período comprendido entre noviembre de 1993 y agosto de 1995. La estabilidad diagnóstica es una medida del grado en que los diagnósticos permanecieron sin cambios en un ingreso posterior. 107 pacientes fueron ingresados más de una vez durante este período. Se encontraron altos niveles de estabilidad diagnóstica para los trastornos psiquiátricos Fl de CIE-10 (100%), esquizofrenia F2 (87%), trastornos bipolares F3 (87%) y trastornos depresivos F3 (73%). Según estos datos la consistencia prospectiva para el trastorno bipolar sería del 87% (IC 95%: 73.2 – 100.7).

6. Amin et al. evaluaron en 1999 la estabilidad de

la psicosis del primer episodio comparando los sistemas ICD-10 y DSM-III-R. El estudio siguió a una cohorte de 168 sujetos con psicosis en un primer episodio, diagnóstico que se realizó por consenso. Después de un seguimiento de tres años, se revaloró un diagnóstico de consenso longitudinal, ciego a los diagnósticos de inicio. Los diagnósticos se basaron en entrevistas de investigación. La estabilidad se midió por los valores predictivos positivos (VPP) de los diagnósticos de inicio, considerándose el sistema más común y preciso sobre la estabilidad del diagnóstico. El estudio analiza diferentes medidas de estabilidad, señalando otras medidas valiosas como la sensibilidad, la especificidad y la cantidad de pacientes adicionales necesarios para prevenir un falso positivo. El estadístico kappa se usó para calcular la concordancia entre los diagnósticos de inicio y seguimiento y muestra un acuerdo moderado en los resultados generales, pero no se calcula específicamente para el trastorno bipolar. Los resultados del estudio mostraron que solo el 78% (IC 95%: 61.4 – 95.1) de los pacientes con diagnóstico inicial de trastorno bipolar por DSM-III-R obtuvieron el mismo diagnóstico a los 3 años de seguimiento, mientras que el 91% (IC 95%: 77.9 – 103.0) de los pacientes con un diagnóstico inicial de CIE-10 de trastorno bipolar (F30-31) obtuvo el mismo diagnóstico en la reevaluación. Sin embargo, solo 21 pacientes se clasificaron inicialmente como psicosis maníaca según la CIE-10, lo que reduce la validez de este hallazgo. Las medidas de estabilidad diagnóstica mostraron datos similares entre los sistemas de clasificación, aunque se encontró una tendencia a una menor sensibilidad en DSM-III-R en comparación con ICD-10.

7. Schwartz et al. realizaron un estudio epidemiológico prospectivo en una cohorte de 547 adultos que vivían en el condado de Suffolk (Nueva York) en el año 2000. Los pacientes reclutados fueron reevaluados 6 y 24 meses después de un diagnóstico de psicosis tras un primer ingreso hospitalario. Los diagnósticos fueron realizados por consenso clínico y siguiendo los criterios del DSM-IV, los psiquiatras eran "ciegos" a los diagnósticos de investigaciones previas. La información provino de la Entrevista Clínica Estructurada para DSM-III-R administrada al inicio y a los 6 y 24 meses de seguimiento, además de los registros médicos. El análisis de la estabilidad diagnóstica se basó en la tabulación cruzada de categorías diagnósticas entre las evaluaciones y estableció dos medidas de estabilidad: consistencia prospectiva y consistencia retrospectiva. La consistencia prospectiva fue la proporción de individuos en una categoría a los 6 meses que conservan la misma categoría de diagnóstico en la evaluación de 24 meses, y correspondería al valor predictivo positivo tomando el diagnóstico de 24 meses como el estándar de oro. La consistencia retrospectiva, que refleja la proporción de sujetos en una categoría a los 24 meses y que previamente recibieron el mismo diagnóstico, representa sensibilidad. La consistencia prospectiva del trastorno bipolar fue alta: 83% (IC 95%: 76.8 – 89.2) y mantuvo la naturaleza distintiva del trastorno. Se encontró una consistencia retrospectiva del 84.8% (IC 95%: 78.8 – 90.8) para el trastorno bipolar. El estudio se centró en los factores asociados con el cambio diagnóstico a la esquizofrenia.

8. Schimmelmann et al. evaluaron, en este estudio de 2005, la estabilidad diagnóstica de los trastornos psicóticos entre 6 semanas y 18 meses después del inicio del tratamiento en una muestra de un primer episodio psicótico. Los sujetos ingresaron en el Centro de Prevención e Intervención de Psicosis Temprana (EPPIC) en Australia de 1998 a 2000. Los datos se obtuvieron de los registros médicos de los pacientes mediante un cuestionario estandarizado. 492 sujetos fueron analizados. se aplicaron criterios DSM-IV. El mismo diagnóstico se realizó al inicio del estudio (< o = 6 semanas después de la admisión en EPPIC) y 18 meses para el 69,9% de los pacientes. Entre los diagnósticos más consistentes se encontraba el trastorno bipolar (83,2%). Llegaron a la conclusión de que es necesario un proceso de diagnóstico longitudinal, especialmente en el trastorno esquizofreniforme y el trastorno bipolar. En este estudio se pueden calcular una consistencia prospectiva de 83.2% (IC 95%: 75.9 – 90.5) y una retrospectiva del 89.2% (IC 95%: 84.3 – 96.3).

9. Un estudio realizado en 2005 por Rufino et al. evaluaba la estabilidad del primer diagnóstico de episodio psicótico en el contexto de las urgencias hospitalarias. La muestra incluyó a 59 pacientes evaluados inicialmente en la unidad de urgencias psiquiátrica (con diagnóstico de urgencia de ingreso y alta) y seguidos durante un período de al menos 12 meses después de la primera evaluación. Durante la admisión de urgencias, se administraron escalas de gravedad y se utilizó la entrevista clínica estructurada para DSM-IV (SCID) en el seguimiento. El acuerdo entre los diagnósticos se calculó mediante el coeficiente kappa. Los diagnósticos de SCID después del seguimiento determinaron cuatro grupos de diagnóstico de urgencia, a saber: trastorno psicótico breve, esquizofrenia, primer episodio maníaco y primer episodio de depresivo. El diagnóstico de episodio maníaco mostró altos niveles de especificidad (100%) pero niveles moderados de sensibilidad (61.5%). Se observó

un patrón similar en el diagnóstico de episodios depresivos (especificidad = 77, 8%, sensibilidad = 98.0%). En este estudio se puede calcular una consistencia prospectiva del 22.6% (IC 95%: 7.9 - 37.3).

10. Amini et al. presentaron en 2005 un trabajo de 48 pacientes con primer episodio psicótico ingresados consecutivamente en el Hospital Roozbeh, Teherán. Los pacientes fueron evaluados al momento del alta hospitalaria y a intervalos de 3, 6 y 12 meses después del ingreso. En cada visita, dos psiquiatras hicieron diagnósticos de consenso DSM-IV y ICD-10, basados en toda la información disponible. La estabilidad se percibió como la consistencia entre los diagnósticos al momento del alta y a los 12 meses de seguimiento. Los trastornos psicóticos afectivos y la esquizofrenia, en ambos sistemas de clasificación, fueron altamente estables. Con los datos aportados en este estudio, la consistencia prospectiva para el trastorno bipolar sería del 100%[1] y la retrospectiva del 94.4% (IC 95%: 83.9 – 105.0).

11. Baldwin et al. presentaron en 2005 un estudio prospectivo con seguimiento durante 6 meses de 194 pacientes con un primer episodio psicótico, de los cuales 30 se diagnosticaron de trastorno bipolar con criterios DSM-IV. La consistencia prospectiva en este estudio para el trastorno bipolar es de 97% (IC 95%: 90.2 – 103.1).

12. Whitty et al. publicaron en 2005 un estudio prospectivo de seguimiento durante cuatro años (de 1995 a 1999) de 147 pacientes con esquizofrenia, trastorno afectivo y otras psicosis que se presentaron con un primer episodio de psicosis. Todos los diagnósticos se realizaron sobre la base de la Entrevista Clínica Estructurada para DSM-IV. Una cuarta parte de los pacientes evidenciaron un cambio en el diagnóstico en el seguimiento. El cambio más común fue al diagnóstico de esquizofrenia. Los valores predictivos positivos de esquizofrenia y trastorno afectivo bipolar fueron 97% y 80% respectivamente. En este caso la consistencia prospectiva para el trastorno bipolar es de 80% (IC 95%: 62.5 – 97.5).

13. Chang et al., en 2009, reportaron un estudio de 166 pacientes de Hong Kong con un primer episodio de psicosis. Los diagnósticos iniciales y finales a los 5 años se realizaron por consenso; se establecieron a través de la revisión sistemática de los registros médicos con criterios CIE-10. El trastorno afectivo bipolar y la esquizofrenia fueron las categorías de diagnóstico más estables. El patrón predominante de cambio diagnóstico fue hacia trastornos del espectro de la esquizofrenia. Con los datos de estudio se pueden calcular, para el trastorno bipolar, una consistencia prospectiva del 100%[1] y retrospectiva del 73.1% (IC 95%: 56.0 – 90.1).

14. Salvatore et al. presentaron en 2011 un estudio realizado entre 1989 y 2003, de 500 pacientes hospitalizados por primeros episodios psicóticos diagnosticados por los criterios de la CIE-10 al inicio del estudio y a los 24 meses. La consistencia prospectiva para la manía psicótica fue del 99% (IC 95%: 97.0 – 100.9) y para el episodio afectivo mixto del 94.9% (IC 95%: 91.4 – 98.3).

15. Bromet et al. reportaron en 2011 una cohorte de 470 pacientes con un primer ingreso por trastornos psicóticos. Se realizaron evaluaciones sistemáticas al inicio del estudio y en los seguimientos de 6 meses, 2 años y 10 años. Los diagnósticos (DSM-III-R y DSM-IV) se formularon después de cada evaluación por consenso de la mejor estimación longitudinal. Los pacientes que inicialmente fueron diagnosticados de trastorno bipolar presentaron una consistencia prospectiva del 69.5% (IC 95%: 60.2 - 78.7).[1] También se calcula una consistencia retrospectiva del 58.4% (IC 95%: 49.3 – 67.5).

16. En otro trabajo de 2011, Kim et al. estudiaron 150 pacientes con trastornos psicóticos que habían ingresado tanto por un primer episodio como por la recurrencia de su psicosis. El diagnóstico de consenso se realizó para cada episodio a través de una revisión de los registros hospitalarios con criterios DSM-IV. El cambio más común fue a trastorno bipolar, y éste representa más de la mitad de todos los cambios diagnósticos. Con los datos aportados en este estudio, la consistencia prospectiva para el trastorno bipolar sería del 86.8% (IC 95%: 76.1 - 97.6)[1] y la retrospectiva del 64.7% (IC 95%: 51.1 - 77.8).

17. Heslin et al. analizaron en 2015 una cohorte poblacional de casos de primer episodio psicótico. Un poco más de la mitad de los casos (59,6%) tenían el mismo diagnóstico CIE-10 inicial y a los 10 años en comparación con el diagnóstico DSM-IV-TR (55,3%), pero la consistencia prospectiva y retrospectiva fue similar. La esquizofrenia, el trastorno bipolar psicótico y la psicosis inducida por fármacos fueron más consistentes prospectivamente que otros diagnósticos. La consistencia prospectiva para el trastorno bipolar fue del 76.4% (IC 95%: 65.1 - 87.6)[1] y la retrospectiva del 67.7% (IC 95%: 56.1 – 79.4).

18. En 2016, Heslin et al. encontraron en una submuestra del estudi anterior, de 360 pacientes con diagnósticos CIE-10, una consistencia prospectiva del 97.1% (IC 95%: 93.2 - 101.0) y un

cambio diagnóstico a trastorno bipolar del 9.7% (IC 95%: 2.9 – 16.6).

AUTORES AÑO	N PAÍS	DISEÑO ESTUDIO TIEMPO SEGUIMIENTO	CRITERIOS DE INCLUSIÓN	CRITERIOS DIAGNÓSTICOS	RESULTADOS (IC 95%)
ESTUDIOS CENTRADOS EN EPISODIOS PSICÓTICOS					
Jørgensen et al. 1988	1136 Dinamarca	Retrospectivo 2 años	- Primer ingreso con psicosis	CIE-8	CP 72.9% (68.5 – 77.4)
Marneros at al. 1991	355 Alemania	Histórico Prospectivo 25.2 años (seguimiento medio)	- Uno de los siguientes episodios al menos una vez: esquizofrénico, melancólico, maníaco, maníaco-depresivo mixto, esquizo-depresivo, esquizofrénico y esquizofrénico-depresivo mixto	DSM-III	CP 62% (29.0 – 96.0)
Hollister et al. 1992	162 USA	Retrospectivo 3 años	- Pacientes ingresados cuatro o más veces	DSM-III-R	CP 52.2% (37.7 – 66.6)
Fennig et al. 1994	278 USA	Prospectivo 6 meses	- Pacientes psicóticos de primera admisión - Diagnóstico de consenso. - Evaluaciones de referencia y semestrales	DSM-III-R	CP 85.7% (75.7 – 94.7) CR 81.9% (71.7 – 90.8)
Daradkeh et al. 1997	107 Emiratos Árabes Unidos	Retrospectivo 2 años	- >1 ingreso por psicosis	CIE-10	CR 87% (73.2 – 100.7)
Amin et al. 1999	168 UK	Prospectivo 3 años	- Psicosis del primer episodio - Diagnóstico de consenso	DSM-III-R CIE-10	CP 78% (61.4 – 95.1) CP 91% (77.9 – 103.0)
Schwartz et al. 2000	547 USA	Prospectivo 2 años	- Primer ingreso de pacientes psicóticos - Evaluaciones basales, 6 y 24 meses	DSM-IV	CP 83% (76.8 – 89.2) CR 84.8% (78.8 – 90.8)
Amini et al. 2005	48 Irán	Prospectivo 1 año	- Primer episodio psicótico	DSM-IV CIE-10	CP 100% CR 94.4% (83.9 – 105.0)
Baldwin et al. 2005	194 Irlanda	Prospectivo 6 meses	- Primer episodio psicótico	DSM-IV	CP 97% (90.2 – 103.1)
Rufino et al. 2005	59 Brasil	Prospectivo 15 meses	- Primer episodio psicótico - Ajuste de emergencia - Seguimiento mínimo de 12 meses	DSM-IV	CP 22.6% (7.9 - 37.3)
Schimmelmann et al. 2005	492 Australia	Retrospectivo 18 meses	- Primer episodio psicótico con ingreso - Reevaluación a los 18 meses	DSM-IV	CP 83.2% (75.9 – 90.5) CR 89.2% (84.3 – 96.3)
Whitty et al. 2005	147 Irlanda	Prospectivo 4 años	- Primer episodio psicótico - Reevaluado a los cuatro años	DSM-IV	CP 80% (62.5 – 97.5)
Chang et al. 2009	166 China	Prospectivo 5 años	- Jóvenes con primer episodio psicótico - Diagnóstico de consenso	CIE-10	CP 100% CR 73.1% (56.0 – 90.1)
Bromet et al. 2011	470 USA	Prospectivo 10 años	- Primer ingreso por psicosis - Diagnóstico de consenso	DSM-III-R DSM-IV	CP 69.5% (60.2 - 78.7) CR 58.4% (49.3 – 67.5)
Kim et al. 2011	150 Korea	Retrospectivo 15 años	- Al menos un ingreso por recaída de episodio psicótico - Diagnóstico de consenso	DSM-IV	CP 86.8% (76.1 - 97.6) CR 64.7% (51.1 - 77.8)
Salvatore et al. 2011	517 USA	Prospectivo 2 años	- Pacientes hospitalizados por un primer episodio psicótico	CIE-10	Manía con psicosis CP 99% (97.0 - 100.9) Episodio afectivo mixto CP 94.9% (91.4 - 98.3)
Heslin et al. 2015	505 Reino Unido	Prospectivo 10 años	- Primer episodio psicótico - Reevaluación a los 10 años - Diagnóstico de consenso	CIE-10 DSM-IV-TR	CP 76.4% (65.1 - 87.6) CR 67.7% (56.1 - 79.4)
Heslin et al. 2016	360 Reino Unido	Prospectivo 10 años	- Primer episodio psicótico - Reevaluación a los 10 años - Diagnóstico de consenso	CIE-10	CP 97.1% (93.2 - 101.0) Cambio diagnóstico a TB 9.7% (2.9 – 16.6)

Tabla 2. Estabilidad diagnóstica del trastorno bipolar centrada en estudios de episodios psicóticos

TB: Trastorno Bipolar. **IC:** Intervalo de confianza. **DSM-IV-TR**: Manual Diagnóstico y Estadístico de Trastornos Mentales, texto revisado. **ICIE-10**: Clasificación Internacional de enfermedades 10ª edición. **TDM**: Trastorno Depresivo Mayor. **CP**: Consistencia Prospectiva. **CR**: Consistencia Retrospectiva. **RDC**: Criterios Diagnósticos de investigación.

A continuación se presentan los trabajos que estudiaron la estabilidad del diagnóstico del trastorno bipolar después de un episodio depresivo:

1. Coryell et al. estudiaron en 1995 a 605 pacientes con trastorno depresivo mayor no bipolar o trastorno esquizoafectivo, tipo deprimido; 96 con trastorno bipolar II; y 231 con trastorno bipolar I o trastorno esquizoafectivo, tipo maníaco. Para este estudio se utilizaron criterios diagnósticos de investigación (RDC en sus siglas en inglés). Solo 20 (5.2%) de los 381 pacientes inicialmente no bipolares que completaron 10 años de seguimiento desarrollaron una manía durante ese tiempo, y solo 19 (5.0%) desarrollaron hipomanía. Así, se encuentra un cambio de diagnóstico a trastorno bipolar del 10.2% (IC 95%: 7.2 - 13.3).

2. Angst et al. presentaron en 2005 un estudio de una cohorte de 406 pacientes con trastornos del estado de ánimo graves hospitalizados en algún momento entre 1959 y 1963; y fueron seguidos hasta 1985. Los diagnósticos se realizaron según criterios CIE-9. Un cambio diagnóstico de depresión a trastorno bipolar I ocurrió en aproximadamente el 1% de los pacientes por año y a trastorno bipolare II en aproximadamente el 0.5% por año. El cambio de diagnóstico global a trastorno bipolar fue del 39.2% (IC 95%: 33.7 - 44.6).

3. Un trabajo se presentó en 2012 por Gilman et al. con modelos de regresión logística para predecir el primer inicio de un episodio maníaco entre 6.214 casos de trastorno depresivo mayor de por vida, según los criterios del DSM-IV. Los pacientes en esta encuesta fueron entrevistados dos veces durante un período de 3 años, en 2000-2001 y en 2004-2005. Aproximadamente 1 de cada 25 individuos con trastorno depresivo mayor hizo la transición al trastorno bipolar durante el período de seguimiento de 3 años del estudio. El cambio de diagnóstico a trastorno bipolar fue del 3.9% (IC 95%: 3.4 - 4.4).

4. Li et al. publicaron en 2012 un estudio de dos cohortes: individuos con trastorno depresivo mayor diagnosticados con criterios CIE-9 durante 2000 (cohorte 2000, n = 1485) y 2003 (cohorte 2003, n = 2459); que fueron reclutados de una cohorte representativa a nivel nacional de 1.000.000 de usuarios de servicios de salud en Taiwán. Los participantes que respondieron bien a los antidepresivos se compararon con aquellos que mostraron respuestas deficientes a los ensayos adecuados de antidepresivos. En el 7,6-12,1% de las personas con diagnóstico de trastorno depresivo mayor unipolar, este diagnóstico se cambió posteriormente a trastorno bipolar, con un tiempo medio de cambio de 1,89 a 2,98 años. Los participantes difíciles de tratar presentaron tasas más altas de cambio a un diagnóstico bipolar (25.6% en la cohorte 2000; 26.6% en la cohorte 2003) que los participantes fáciles de tratar (8.8-8.9% en la cohorte 2000; 6.8-8.6% en la cohorte 2003; P <0,0001). Así, se encuentró un cambio global de diagnóstico a trastorno bipolar del 10.0% (IC 95%: 8.5 - 11.5) para la cohorte 2000 y del 12.1% (IC 95%: 10.8 - 13.4) para la cohorte 2003.

5. Dudek et al. revisaron en 2013 una muestra de 122 pacientes con diagnóstico primario de trastorno depresivo mayor; se utilizaron criterios CIE-9 y CIE-10. La conversión diagnóstica de trastorno depresivo mayor en trastorno bipolar se observó en el 32.8% (IC 95%: 24.4 - 41.1) de los pacientes. El tiempo medio de conversión fue de 9.27 ± 8.64 años.

6. Østergaard et al. reportaron en 2014 un estudio prospectivo de una cohorte histórica de registros daneses. Los pacientes con diagnóstico CIE-10 de depresión psicótica fueron seguidos entre 1995 y 2007. Se identificaron 8.588 pacientes con depresión psicótica, de los cuales el 7,1%, (IC 95%: 6.5 - 7.6) desarrollaron un trastorno bipolar durante el seguimiento.

7. En el estudio de 2015 de James et al. basado en los registros de la Estadística de Episodios Hospitalarios (HES en sus siglas en inglés), que cubre todos los ingresos hospitalarios y hospitalizaciones del Servicio Nacional de Salud inglés entre 1999 y 2011. Para este estudio se utilizaron criterios CIE-10. La tasa general de conversión de depresión a trastorno bipolar para todas las edades fue del 5,65% (IC 95%: 5,4 - 5,8) durante un período mínimo de seguimiento de 4 años.

8. Nakamura et al., en 2015, evaluaron retrospectivamente 89 pacientes hospitalizados por depresión grave (diagnosticados según la CIE-10) con y sin síntomas psicóticos de 2001 a 2010. Tras 75 meses de evaluaciones de seguimiento el 12.3% (IC 95%: 5.5 - 19.1) de los pacientes habían desarrollado un trastorno bipolar.

9. Woo et al. presentaron en 2015 los registros médicos de 250 pacientes con diagnóstico de trastorno depresivo mayor, con criterios DSM-IV, que durante al menos 5 años fueron revisados retrospectivamente para este estudio. La conversión diagnóstica de trastorno depresivo mayor a trastorno bipolar se observó en el 18,4% (IC 95%: 13.5 - 23.2) de los pacientes. Los criterios diagnósticos para trastorno de espectro

bipolar predijeron esta conversión con alta sensibilidad (0,87) y especificidad (0,91).

10. Heslin et al. presentaron en 2016 un estudio de una cohorte de primer episodio psicótico que fue seguida durante 10 años después de la primera presentación. Con criterios CIE-10 se diagnosticaron, al inicio, 62 pacientes con depresión mayor psicótica, 218 pacientes con esquizofrenia y 70 pacientes con trastorno bipolar psicótico/manía. Con los datos aportados en este estudio se puede calcular una consistencia prospectiva para el trastorno bipolar del 97.1% (IC 95%: 93.2 - 101.0) y un cambio de diagnóstico de depresión mayor psicótica a trastorno bipolar del 9.7% (IC 95%: 2.9 – 16.6).

11. Bukh et al. evaluaron en 2016 un total de 301 pacientes hospitalarios o ambulatorios de entre 18 y 70 años con un diagnóstico validado (criterios CIE-10) de un primer episodio depresivo entre 2005 y 2007. A los 5 años de seguimiento los pacientes fueron reevaluados, de 2011 a 2013, mediante el método del gráfico de vida. y entrevistas de diagnóstico. A los 5 años el 8,6% (IC 95%: 5.5 - 11.8) de los pacientes fueron diagnosticados de trastorno bipolar (6,3% en los primeros 2 años).

AUTORES AÑO	N PAÍS	DISEÑO ESTUDIO TIEMPO SEGUIMIENTO	CRITERIOS DE INCLUSIÓN	CRITERIOS DIAGNÓSTICOS	RESULTADOS (IC 95%)
ESTUDIOS CENTRADOS EN DEPRESIÓN					
Coryell et al. 1995	932 USA	Prospectivo 5-10 años	- Pacientes internos y externos tratados por trastornos afectivos - Mayores de 17 años - CI >70	RDC	Cambio diagnóstico a TB 10.2% (7.2 - 13.3)
Angst et al. 2005	406 Suiza	Prospectivo 26 años	- Pacientes hospitalizados con manía, depresión endógena, depresión endo-reactiva, trastorno maníaco-depresivo, trastorno afectivo con características psicóticas incluyendo trastorno esquizoafectivo	CIE-9	Cambio diagnóstico a TB 39.2% (33.7 - 44.6)
Gilman et al. 2012	6.214 USA	Prospectivo 3 años	- Diagnóstico de TDM	DSM-IV	Cambio diagnóstico a TB 3.9% (3.4 - 4.4)
Li et al. 2012	2 cohortes: n= 1485 de 2000 a 2007 n= 2459 de 2003 a 2007 Taiwán	Prospectivo 8 años	- Todos los pacientes adultos de la base de datos del Seguro de Salud Nacional diagnosticados por psiquiatras de TDM	CIE-9	Cambio diagnóstico a TB 10.0% (8.5 - 11.5) 2000 - 2007 12.1% (10.8 - 13.4) 2003 – 2007
Dudek et al. 2013	122 Polonia	Retrospectivo 30 años	- Edad > 18 años al inicio - Primer diagnóstico establecido de depresión	CIE-9 CIE-10	Cambio diagnóstico a TB 32.8% (24.4 - 41.1)
Østergaard et al. 2014	8.588 Dinamarca	Prospectivo 12 años	- Pacientes con diagnóstico de depresión psicótica a partir de registros daneses	CIE-10	Cambio diagnóstico a TB 7.1% (6.5 - 7.6)
James et al. 2015	69792 Reino Unido	Retrospectivo 4-12 años	- Diagnóstico clínico de depresión a partir de un conjunto de datos vinculados de las Estadísticas de Episodios de Hospitales Nacionales ingleses.	CIE-10	Cambio diagnóstico a TB 5.65% (5.4 – 5.8)
Nakamura et al. 2015	89 Japón	Retrospectivo 9 años	- Pacientes hospitalizados por depresión severa con y sin psicosis	CIE-10	Cambio diagnóstico a TB 12.3% (5.5 - 19.1)
Woo et al. 2015	250 Corea	Retrospectivo 5 años	- Historiales médicos de pacientes con TDM	DSM-IV	Cambio diagnóstico a TB 18.4% (13.5 - 23.2)
Bukh et al. 2016	301 Dinamarca	Prospectivo 5 años	- Primer episodio depresivo	CIE-10	Cambio diagnóstico a TB 8.6% (5.5 - 11.8)

Tabla 3. Estabilidad diagnóstica de estudios centrados en depresión

TB: Trastorno Bipolar. **IC:** Intervalo de confianza. **DSM-IV-TR**: Manual Diagnóstico y Estadístico de Trastornos Mentales, texto revisado. **ICIE-10**: Clasificación Internacional de enfermedades 10ª edición. **TDM**: Trastorno Depresivo Mayor. **CP**: Consistencia Prospectiva. **CR**: Consistencia Retrospectiva. **RDC**: Criterios Diagnósticos de investigación.

Finalmente, se presentan estudios que evaluaron la estabilidad del diagnóstico del trastorno bipolar en relación con patología psiquiátrica en general:

1. Tsuang et al. en 1981, estudian a 1578 familiares de primer grado de esquizofrénicos, maníacos, depresivos y controles; fueron entrevistados personalmente usando el Formulario de Entrevista Psiquiátrica Estructurada de Iowa, sin conocimiento de los diagnósticos psiquiátricos. Para realizar diagnósticos se utilizaron *Feighner Criteri*a. Con los datos aportados en este estudio, la consistencia prospectiva para el trastorno bipolar sería del 56.0% (IC 95%: 35.5 – 75.5%) cuando se valora la entrevista estructurada y del 80.4% (IC 95%: 64.0% to 96.8%) cuando se valoran las notas clínicas.

2. Atwoli et al. compararon 2012 los diagnósticos de ingreso y alta de una muestra consecutiva de 114 pacientes psiquiátricos ingresados de nuevo. Los diagnósticos, realizados con criterios DSM-IV-R, más frecuentes en el momento del ingreso fueron los trastornos del espectro de la esquizofrenia (47,4%) y los trastornos del espectro bipolar (30,7%). La estabilidad diagnóstica general medida por la consistencia prospectiva en este estudio fue de 72.8%, la categoría diagnóstica más estable fue el trastorno depresivo mayor (100% de consistencia prospectiva y retrospectiva), seguido por el trastorno bipolar con un 91.4% de (IC 95%: 82.1 - 100.7) de consistencia prospectiva y un 69.6% (IC 95%: 56.2 - 82.9) de consistencia retrospectiva.

3. Alavi et al. publicaron en 2014 un estudio sobre 485 pacientes adultos readmitidos en el hospital. Todos los diagnósticos se realizaron de acuerdo con el DSM-IV-TR. Los diagnósticos más frecuentes en el primer ingreso fueron el trastorno bipolar (48,5%) y el trastorno depresivo mayor (18,8%). El diagnóstico más estable fue el trastorno bipolar: 71% (IC 95%: 66.9 - 74.9) de consistencia prospectiva y 69,4% (IC 95%: 65.4 - 73.6) de consistencia retrospectiva.

AUTORES AÑO	N PAÍS	DISEÑO ESTUDIO TIEMPO SEGUIMIENTO	CRITERIOS DE INCLUSIÓN	CRITERIOS DIAGNÓSTICOS	RESULTADOS (IC 95%)
ESTUDIOS CENTRADOS EN TRASTORNOS PSIQUIÁTRICOS EN GENERAL					
Tsuang et al. 1981	445 USA	Prospectivo 30-40 años	- Pacientes ingresados por Esquizofrenia y Trastornos Afectivos - Diagnóstico de consenso	Criterios Feighner	CP 56.0% (35.5 - 75.5%) Entrevista CP 80.4% (64.0% -96.8%) Registro
Atwoli et al. 2012	114 Kenia	Prospectivo Respuesta 35 días	- Al menos un ingreso psiquiátrico previo	DSM IV TR	CP 91.4% (82.1 - 100.7) CR 69.6% (56.2 - 82.9)
Alavi et al. 2014	485 Irán	Retrospectivo 12 años	- Al menos un ingreso psiquiátrico previo	DSM-IV-TR	CP 71% (66.9 - 74.9) CR 69.4% (65.4 - 73.6)

Tabla 4. Estabilidad diagnóstica de estudios centrados en trastornos psiquiátricos en general
TB: Trastorno Bipolar. **IC:** Intervalo de confianza. **DSM-IV-TR**: Manual Diagnóstico y Estadístico de Trastornos Mentales, texto revisado. **ICIE-10**: Clasificación Internacional de enfermedades 10ª edición. **TDM**: Trastorno Depresivo Mayor. **CP**: Consistencia Prospectiva. **CR**: Consistencia Retrospectiva. **RDC**: Criterios Diagnósticos de investigación.

3.4.3 Tendencias de futuro

Varios estudios han sugerido que los cambios estructurales permanentes en el cerebro pueden estar asociados con el trastorno bipolar (Fagiolini et al. 2005; Savitz et al. 2005; Malhi et al. 2005; Malhi et al. 2007). Los pacientes eutímicos bipolares han mostrado una disminución de la activación en respuesta a los estímulos afectivos tanto en las regiones corticales como en las subcorticales del cerebro en comparación con los sujetos sanos, y tal vez están limitados en su capacidad de realizar un

procesamiento emocional (Malhi et al. 2005). Se ha descubierto que la función psicosocial se ve comprometida por los déficits cognitivos relacionados con el estado de ánimo tanto en la depresión bipolar como en la hipomanía (Malhi et al. 2007). Los individuos diagnosticados de trastorno bipolar, tanto en la fase aguda como en la eutimia de la enfermedad, muestran déficits en un rango de tareas neuropsicológicas, y se reportan correlaciones entre el número experimentado de episodios afectivos y el desempeño de la tarea (Fagiolini et al. 2005). Se ha reportado la existencia de déficits de atención, aprendizaje y memoria, y de función ejecutiva (Savitz et al. 2005). Además, la investigación neuropsicológica de los jóvenes con trastorno bipolar sugiere que. las mismas anomalías presentes en los adultos que padecen trastorno bipolar, también pueden estar presentes en los niños (Cahill et al. 2007; Doyle et al. 2005).

Estos hallazgos han fomentado el interés existente en el perfil neuropsicológico de los individuos con trastorno bipolar. La evolución del trastorno bipolar puede, por tanto, ser comparable a los modelos de trastorno neurodegenerativo que causan degeneración neuronal progresiva y dan lugar a un cierto nivel de discapacidad (Figura 2). Algunos estudios han señalado el uso futuro de los biomarcadores como la forma de asegurar la detección precoz de la enfermedad preclínica o clínica y proporcionar la oportunidad de iniciar una terapia preventiva o precoz. Los biomarcadores (a través de la genética, las manifestaciones clínicas, la neuroimagen o la bioquímica) pueden ayudar a identificar grupos de riesgo, acelerar y mejorar la precisión de los diagnósticos y favorecer el desarrollo de tratamientos farmacológicos (DeKosky et al. 2003).

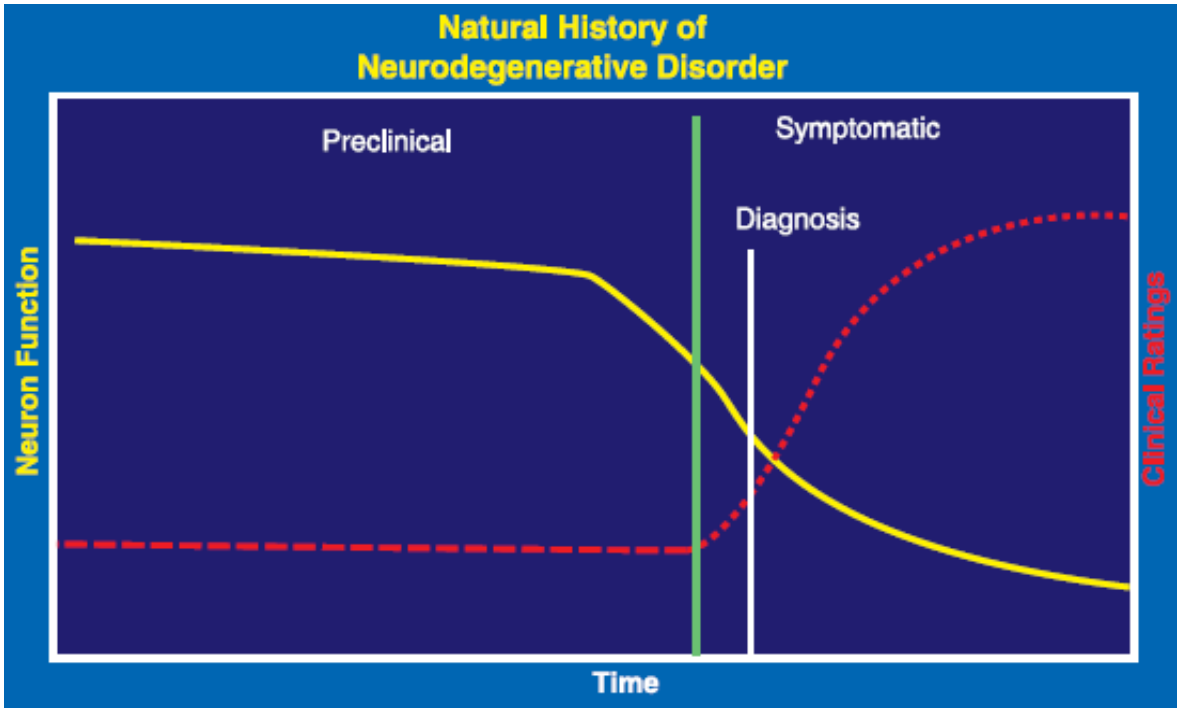

Figura 2. Modelo para la progresión de la pérdida de la función neuronal en los trastornos neurodegenerativos.
Tomado de DeKosky 2003.

En estudios de neuroimagen funcional con pacientes bipolares (Frangou 2019) se ha hallado un descenso de actividad en corteza prefrontal durante procesos cognitivos y un aumento de actividad en regiones subcorticales límbicas durante procesos emocionales.

En estudios de neuroimagen estructural volumétrica (Blumberg et al. 2003) también se observa en los pacientes con trastorno bipolar una disminución de volumen de la sustancia gris prefrontal ventral y orbital media, y un aumento del volumen de la sustancia gris estriatal y de la amígdala.

Al igual que en esquizofrenia (Sanz-Fuentenebro et al. 2013), también se han realizado estudios de imagen para estudiar la integridad celular a nivel cerebral en pacientes con trastorno bipolar, para lo que se ha empleado la resonancia magnética espectroscópica protónica (RME^{1}H) (Figura 3). Esta técnica permite el estudio de diversos componentes bioquímicos directamente in vivo, posibilitando la medida de moléculas

como el N-acetilaspartato (NAA), colina (Cho), creatina (Cr) o inositol (Ino) (Urenjak et al. 1993). El NAA se ha empleado como un marcador de integridad neuronal. Se encuentra principalmente en las neuronas, más que en las células gliales (Miller 1991; Tsai et Coyle 1995). Así, la disminución de NAA se ha identificado como un dato indirecto de la pérdida de neuronas y axones y/o disfunción neuronal (DeStefano et al. 1995; Tsai et Coyle 1995). En la literatura hay estudios que muestran unos niveles de NAA o del cociente NAA/Cr disminuidos en lóbulo prerontal dosrsolateral (LPFDL) de bipolares eutímicos (Winsberg et al. 2000; Chang et al. 2003; Sassi et al. 2005; Molina et al. 2007; Olvera et al. 2007). También se ha observado un incremento en los niveles de NAA o del cociente NAA/Cr tras el tratamiento con litio en pacientes bipolares en diversas zonas, como el LPFDL, el cingulado anterior o el lóbulo parietal (Stoll et al. 1992; Hamakawa et al. 1999; Moore, et al. 2000; Silverstone et al. 2003; Brambilla et al. 2005; Amaral et al. 2006). Otros trabajos no han hallado diferencias estadísticamente significativas de NAA o del cociente NAA/Cr tras el tratamiento con litio, en LPFDL en episodios de manía (Frey et al. 2005; Michael et al. 2003), en niños bipolares (Gallelli et al. 2005) ni tras tratamiento con litio (Brambilla et al. 2004).

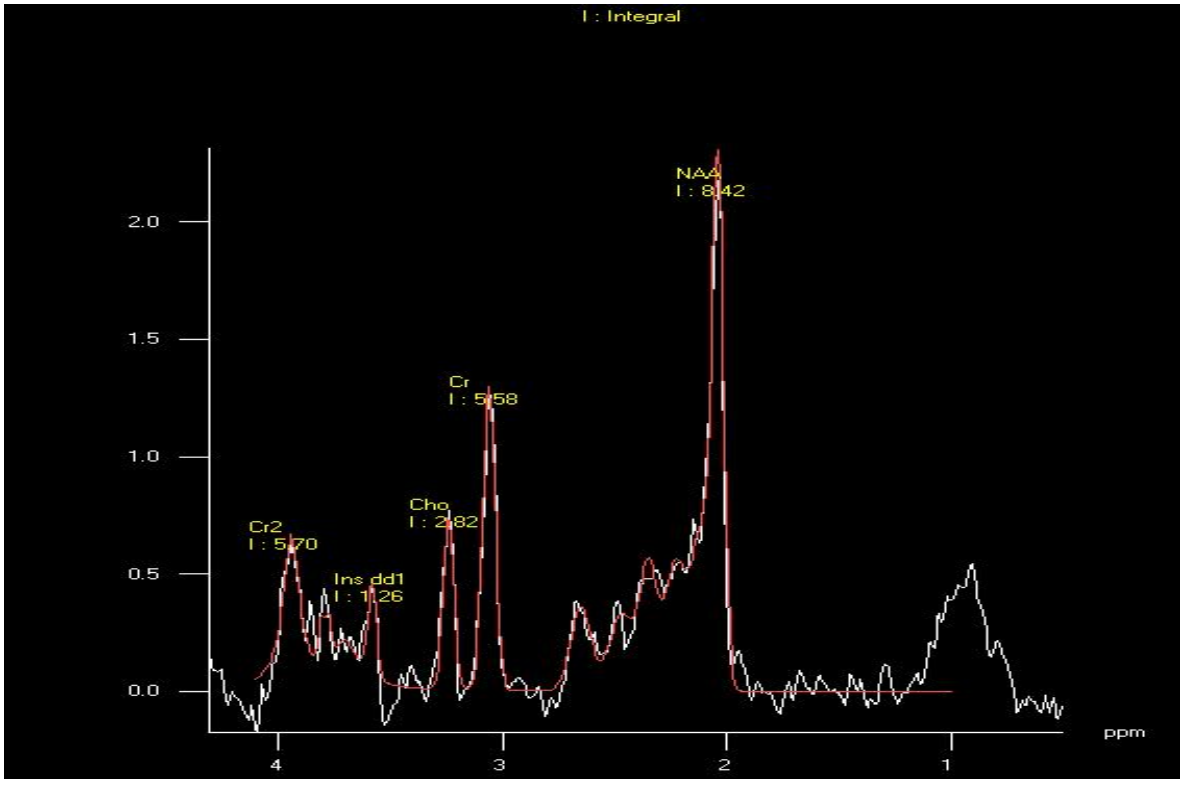

Figura 3. Gráfico de resonancia magnética espectroscótica.
Cr y Cr^2: Creatina. **Ins**: Inositol. **Cho**: Colina. **NAA**: N-acetil-aspartato.

La evidencia en la literatura sugiere que existe un deterioro sustancial en los pacientes con trastorno bipolar, incluso cuando no han experimentado más de dos episosios depresivos o maníacos durante un período relativamente largo, y cuando los pacientes tienen un nivel de educación relativamente alto y no abusan de sustancias (Fagiolini et al. 2005; Blumberg et al. 2003). Los endofenotipos candidatos a la función cerebral incluyen déficit de atención, déficit en el aprendizaje verbal y la memoria, déficit cognitivo después del agotamiento del triptófano, inestabilidad del ritmo circadiano y dismodulación de la motivación y la recompensa (Hasler et al. 2006). La detección precoz de la enfermedad cobra especial importancia a la vista de estos hallazgos (Cahill et al. 2007). La mejora de los procedimientos diagnósticos a través de la evaluación longitudinal de los pacientes puede jugar un papel crucial en la corrección de las deficiencias reales en la detección y tratamiento de la enfermedad. La sabiduría sobre los factores relacionados con el cambio diagnóstico, las vías de diagnóstico habituales y las consecuencias clínicas de la inestabilidad diagnóstica aún está lejos de ser perfecta.

4 OBJETIVOS E HIPÓTESIS

Resumen

El objetivo principal del presente estudio es realizar una evaluación ecológica de la estabilidad diagnóstica del trastorno bipolar en la Comunidad de Madrid. Otros objetivos de este estudio son determinar la consistencia temporal del diagnóstico, las variables personales que influyen en que éste se realice de forma estable y la prevalencia del trastorno bipolar en esta comunidad autónoma. Se postula la hipótesis de que existen dificultades para diagnosticar el trastorno bipolar y que su estabilidad diagnóstica se puede lograr con múltiples evaluaciones a lo largo de un período prolongado de tiempo. Se establece de forma arbitraria un 75% de coincidencia diagnóstica en las evaluaciones para considerar un diagnóstico como estable.

4.1 OBJETIVOS

El objetivo principal del presente estudio es realizar una evaluación ecológica, en consultas ambulatorias psiquiátricas de la Comunidad Autónoma de Madrid, de la estabilidad a largo plazo del trastorno bipolar según la Clasificación Internacional de Enfermedades - 10ª edición.

El estudio contribuye a conocer la consistencia temporal del trastorno bipolar y los cambios diagnósticos habituales que se producen a lo largo de la enfermedad, estableciendo así la base para futuras investigaciones sobre la evolución de los diagnósticos y las causas de los cambios diagnósticos.

Un objetivo secundario de este trabajo es determinar qué variables sociodemográficas están relacionadas con la estabilidad del diagnóstico de trastorno bipolar. Esto podría ayudar a realizar un diagnóstico más fiable, sobre todo en las primeras evaluaciones de los pacientes.

Otro objetivo de este estudio, dado que en los Centros de Salud Mental se da cobertura sanitaria a la gran mayoría de la población de la Comunidad de Madrid, es establecer la prevalencia del trastorno bipolar en esta comunidad; también, comparar esta prevalencia con las reportadas en la literatura.

4.2 HIPÓTESIS

Se postula que existen dificultades para diagnosticar el trastorno bipolar, y que se producen errores diagnósticos tanto por exceso como por defecto.

La validez del diagnóstico de trastorno bipolar viene determinada por su estabilidad diagnóstica durante múltiples evaluaciones a lo largo de un período prolongado de tiempo. El grado en el que un paciente es clasificado consistentemente como un trastorno bipolar durante el seguimiento es un marcador importante para la validez del diagnóstico en sí mismo.

El 75% de coincidencia en las evaluaciones a lo largo del seguimiento podría representar un punto de corte adecuado para determinar la existencia de estabilidad diagnóstica.

La consistencia temporal del trastorno bipolar puede haber sido sobreestimada por estudios previos. Son necesarios estudios que contengan múltiples puntos de evaluación, períodos largos de seguimiento y muestras extensas para verificar los resultados anteriores.

La consistencia prospectiva y retrospectiva de un diagnóstico (entre el primer y el último diagnóstico) es útil para evaluar el grado inicial y final de diagnóstico erróneo de un trastorno.

5 MATERIAL Y MÉTODOS

Resumen

En este estudio se han recogido los datos aportados por el Registro Acumulativo de Casos de la Comunidad de Madrid, desde 1980 a 2009, en los Centros de Salud Mental de esta comunidad. Este registro recoge el conjunto mínimo básico de datos y utiliza códigos diagnósticos CIE. Se seleccionaron 14.557 pacientes que fueron diagnosticados al menos una vez de trastorno bipolar, que hubiesen tenido al menos 10 visitas durante el período de estudio y un mínimo de un año de seguimiento. Para estudiar la estabilidad diagnóstica se midieron dos índices complementarios: la consistencia temporal y la constancia diagnóstica (75% de las visitas con diagnóstico de trastorno bipolar). Se analizaron tanto la consistencia prospectiva como la consistencia retrospectiva, así como el coeficiente kappa de acuerdo diagnóstico entre la primera y la última evaluación. Para el análisis estadístico se empleó el programa *Statistical Package for the Social Sciences*, versión 27.0; se midió la consistencia temporal de los diagnósticos de trastorno bipolar y se comparó la prevalencia de diferentes diagnósticos psiquiátricos entre aquellos con trastorno bipolar estable. Los análisis estadísticos se realizaron en dos pasos para buscar los determinantes de la inestabilidad: análisis univariados seguidos de un análisis multivariante mediante regresión logística.

5.1 FUENTE DE DATOS

Los centros públicos de salud mental de la provincia de Madrid, España, han registrado todas las visitas de Salud Mental en un registro regional ("Registro Acumulativo de Casos de la Comunidad de Madrid"). De 1980 a 1992, los diagnósticos se codificaron de acuerdo con la Clasificación Internacional de Enfermedades, Novena Revisión (CIE-9) (World Health Organitation (WHO), 1978). Desde 1992, los diagnósticos se codificaron de acuerdo con la Clasificación Internacional de Enfermedades, Décima Revisión (CIE-10) (WHO 1992). En la base de datos utilizada para nuestros análisis se identificó de forma fiable a los usuarios individuales de los servicios, ya que a cada paciente se le asignó un número de identificación (se utilizó un código numérico para garantizar el anonimato del paciente). Para asegurarnos de que a ningún paciente se le hubiera asignado más de un identificador, revisamos todos los casos de la base de datos y eliminamos todos los duplicados que encontramos. Se definieron los duplicados como `pacientes con idéntico nombre, apellido, sexo y año de nacimiento'; `pacientes con idéntico nombre, apellido, sexo y dirección', o `pacientes con idéntico nombre, apellido, sexo y número de registro hospitalario/ambulatorio'. Eliminamos todos los casos en los que existía una sospecha significativa de duplicación. Un número de identificación único (Baca-Garcia et al. 2007) asignado a cada usuario de los servicios garantizaba el anonimato de los pacientes y permanecía inalterado en todos las valoraciones.

5.1.1 Base de datos

Se extrajeron los datos del registro regional de todas las visitas se salud mental a todos los Centros de Salud Mental de la Comunidad de Madrid, desde el 6 de enero de 1980 hasta el 29 de diciembre de 2009. En esta comunidad autónoma se da cobertura sanitaria a una población, en ese período de recogida de datos, de entre 4,727 y 6,387 millones de personas (según el Instituto Nacional de Estadística) y forma parte de los Servicios Nacionales de Salud españoles, que se financian mediante impuestos para prestar asistencia sanitaria gratuita a todos los ciudadanos españoles y a los inmigrantes legales. En los 30 años del período de estudio, 691.526 pacientes recibieron atención en salud mental con hasta un total de 8.074.488 evaluaciones. Se evaluaron 21.674 pacientes con diagnóstico de trastorno bipolar en alguna de las valoraciones, un 3,1% de la muestra total, con al menos un diagnóstico de trastorno bipolar durante el período de estudio, que recibieron 884.999 consultas, que representan un 10,9% del total de consultas de Salud Mental ambulatorias en la Comunidad de Madrid.

5.1.2 Recogida de datos

La recogida de datos se realizó de forma sistemática en todos los Centros de Salud Mental de la Comunidad de Madrid. Esta recogida se realizaba tras todas las consultas ambulatorias de Salud Mental y, entre otros datos, se recogía los diagnósticos prevalentes para el paciente en esa consulta. Esta recogida de datos se realizó mediante un registro acumulativo de casos atendidos en los Centros de Salud Mental de la Comunidad de Madrid. Este registro recoge el conjunto mínimo básico de datos (CMBD) definido por la Comunidad de Madrid (ver Anexo I). Este registro utiliza códigos diagnósticos CIE. Los registros que se codificaron con criterios CIE-9 se recodificaron a diagnósticos CIE-10. Para ello se emplearon tablas de conversión entre la CIE-9 y la CIE-10, siguiendo los criterios de la Organización Mundial de la Salud (WHO 1993).

5.1.3 Muestra

Los participantes fueron seleccionados de la muestra de pacientes mayores de 18 años de edad que fueron valorados en los Centros de Salud

Mental de la Comunidad de Madrid en el período de recogida sistemática de datos, un total de 691.526 pacientes que recibieron 8.047.488 consultas con registro CMBD. De esta muestra se seleccionaron aquellos que fueron diagnosticados al menos una vez de trastorno bipolar (N=21.674). De esta submuestra se selecionaron aquellos pacientes que hubiesen tenido al menos 10 visitas durante el período de estudio y un mínimo de un año de seguimiento (N=14.557). Estas medidas se adoptaron para garantizar una mayor fiabilidad en el proceso diagnóstico y se descartaron 7.117 pacientes en los que el tiempo de seguimiento fue menor a un año o recibieron menos de 10 evaluaciones en la consulta ambulatoria. Teniendo en cuenta las dificultades diagnósticas del trastorno bipolar, se excluyeron a estos pacientes para evitar sesgos diagnósticos y homogeneizar la muestra a estudio. Así, se seleccionaron un total de 14.557 pacientes que recibieron un diagnóstico de trastorno bipolar según criterios CIE-10, en al menos una evaluación, en seguimiento durante al menos un año y que fueron valorados en al menos 10 ocasiones. Estos 14.557 pacientes tuvieron 848.147 consultas de Salud Mental. La duración media del seguimiento de estos pacientes fue de 3.295,9 días (desviación estándar (DE) 1.967,6 días) y la media de visitas fue de 58,3 (con un rango entre 10-1.449). El estudio no requirió la conformidad informada de los pacientes ya que no se realizó ninguna intervención adicional sobre ellos y el anonimato ha sido garantizado mediante el uso de un sistema de codificación numérica con asignación de un número de registro relacional.

5.1.4 Procedimientos diagnósticos

Los facultativos que asignaron los diagnósticos son psiquiatras y psicólogos del sistema sanitario público de la Comunidad de Madrid, la mayoría de ellos con muchos años de de práctica clínica y experiencia de trabajo en Centros de Salud Mental. Los diagnósticos se realizaron según la práctica clínica habitual: principalmente basada en la entrevista clínica con el paciente, pero también teniendo en cuenta la información disponible, incluyendo los datos de los registros médicos, otras evaluaciones de otros ámbitos clínicos y entrevistas con los familiares. Para la codificación de los diagnóstico se utilizó la CIE-9 y CIE-10. La mayoría de los facultativos de Salud Mental en España, y por ende en la Comunidad de Madrid, tienen un buen conocimiento del sistema CIE, tanto de su 9ª como su 10ª edición.

5.1.5 Los responsables del diagnóstico

Los diagnósticos fueron realizados por psiquiatras y/o psicólogos de acuerdo con la CIE-9 o CIE-10, dependiendo de la fecha de evaluación. Los facultativos tratantes tenían una formación clínica estándar en evaluación diagnóstica y fueron contratados por el Sistema Nacional de Salud Mental. Los facultativos responsables tenían una amplia experiencia en la evaluación y el tratamiento de pacientes. Estos facultativos registraron un máximo de 2 diagnósticos por paciente por visita con fines administrativos y no vieron el proceso del estudio.

5.1.6 Grupos diagnósticos incluidos en el análisis estadístico

Además del trastorno bipolar (CIE-10 F31) y el episodio maníaco (CIE-10 F30), se incluyeron todos los bloques del capítulo V de la CIE-10 [Trastornos mentales y de la conducta (F00-F99)] (categorías de dos dígitos, Fx) en el análisis.

Se realizó un análisis tanto por categorías diagnósticas Fx como la relación de éstas con el diagnóstico de trastorno bipolar a lo largo las diferentes evaluaciones a lo largo del seguimiento de cada paciente.

Diagnósticos incluidos en las categorías de Episodio maníaco (CIE-10 F30) y de Trastorno bipolar (CIE-10 F31):

- F30 Episodio maníaco:
- F30.1 Episodio maníaco sin síntomas psicóticos
- F30.10 Episodio maníaco sin síntomas psicóticos, no especificado
- F30.11 Episodio maníaco sin síntomas psicóticos, leve
- F30.12 Episodio maníaco sin síntomas psicóticos, moderado
- F30.13 Episodio maníaco, grave, sin síntomas psicóticos
- F30.2 Episodio maníaco, grave, con síntomas psicóticos
- F30.3 Episodio maníaco en remisión parcial
- F30.4 Episodio maníaco en remisión completa
- F30.8 Otros episodios maníacos
- F30.9 Episodio maníaco, no especificado

- F31 Trastorno bipolar:
- F31.0 Trastorno bipolar, episodio actual hipomaníaco
- F31.1 Trastorno bipolar, episodio actual maníaco sin síntomas psicóticos
- F31.10 Trastorno bipolar, episodio actual maníaco, sin síntomas psicóticos, no especificado
- F31.11 Trastorno bipolar, episodio actual maníaco, sin síntomas psicóticos, leve
- F31.12 Trastorno bipolar, episodio actual maníaco, sin síntomas psicóticos, moderado
- F31.13 Trastorno bipolar, episodio actual maníaco, sin síntomas psicóticos, grave

- F31.2 Trastorno bipolar, episodio actual maníaco, con síntomas psicóticos, grave
- F31.3 Trastorno bipolar, episodio actual depresivo, gravedad leve o moderada
- F31.30 Trastorno bipolar, episodio actual depresivo, gravedad leve o moderada, no especificado
- F31.31 Trastorno bipolar, episodio actual depresivo, leve
- F31.32 Trastorno bipolar, episodio actual depresivo, moderado
- F31.4 Trastorno bipolar, episodio actual depresivo, grave, sin síntomas psicóticos
- F31.5 Trastorno bipolar, episodio actual depresivo, grave, con síntomas psicóticos
- F31.6 Trastorno bipolar, episodio actual mixto
- F31.60 Trastorno bipolar, episodio actual mixto, no especificado
- F31.61 Trastorno bipolar, episodio actual mixto, leve
- F31.62 Trastorno bipolar, episodio actual mixto, moderado
- F31.63 Trastorno bipolar, episodio actual mixto, grave, sin síntomas psicóticos
- F31.64 Trastorno bipolar, episodio actual mixto, grave, con síntomas psicóticos
- F31.7 Trastorno bipolar, actualmente en remisión
- F31.70 Trastorno bipolar, actualmente en remisión, episodio más reciente no especificado
- F31.71 Trastorno bipolar, en remisión parcial, episodio más reciente hipomaníaco
- F31.72 Trastorno bipolar, en remisión completa, episodio más reciente hipomaníaco
- F31.73 Trastorno bipolar, en remisión parcial, episodio más reciente maníaco
- F31.74 Trastorno bipolar, en remisión completa, episodio más reciente maníaco
- F31.75 Trastorno bipolar, en remisión parcial, episodio más reciente depresivo
- F31.76 Trastorno bipolar, en remisión completa, episodio más reciente depresivo
- F31.77 Trastorno bipolar, en remisión parcial, episodio más reciente mixto
- F31.78 Trastorno bipolar, en remisión completa, episodio más reciente mixto
- F31.8 Otros trastornos bipolares
- F31.81 Trastorno bipolar II
- F31.89 Otros tipos de trastorno bipolar
- F31.9 Trastorno bipolar, no especificado

Las categorías Fx incluidas en el análisis del presente estudio se corresponen a las del capítulo V de la CIE-10, Trastornos mentales y del comportamiento:

- F00–F09 Trastornos mentales orgánicos, incluidos los trastornos sintomáticos
- F10–F19 Trastornos mentales y del comportamiento debidos al uso de sustancias psicoactivas.
  F20–F29 Esquizofrenia, trastornos esquizotípicos y trastornos delirantes.
- F30–F39 Trastornos del humor [afectivos].
  F40–F48 Trastornos neuróticos, trastornos relacionados con el estrés y trastornos somatomorfos.
  F50–F59 Síndromes del comportamiento asociados con alteraciones fisiológicas y factores físicos.
  F60–F69 Trastornos de la personalidad y del comportamiento en adultos.
- F70–F79 Retraso mental.
  F80–F89 Trastornos del desarrollo psicológico
  F90–F98 Trastornos emocionales y del comportamiento que aparecen habitualmente en la niñez y en la adolescencia.
- F99 Trastorno mental no especificado.

5.2 ESTRATEGIA DEL ANÁLISIS

5.2.1 Estabilidad diagnóstica

A través de todas las evaluaciones se calculó la estabilidad diagnóstica según Schwartz et al. y Baca-García et al. (Schwartz et al. 2000; Baca-Garcia et al. 2007) con métodos estadísticos tradicionales utilizando la versión 27.0 de SPSS (*Statistical Package for the Social Sciences*, versión 27.0; SPSS Inc., Chicago, IL, USA). Se utilizaron dos índices complementarios de estabilidad diagnóstica para aumentar la coherencia de nuestros resultados:

1. Consistencia temporal

La consistencia temporal es la presencia o ausencia de un trastorno particular en dos momentos diferentes (Pettit et al. 2005). Se utilizaron tres medidas diferentes de consistencia temporal para el trastorno bipolar (Schwartz et al. 2000). La primera, "consistencia prospectiva", es la proporción de individuos en una categoría en la primera evaluación que permanecen en la misma categoría en su última evaluación. Esto correspondería a un valor predictivo positivo si el último diagnóstico fuera el patrón oro. Es clínicamente útil porque indica hasta qué punto un diagnóstico dado en la evaluación inicial estará presente en la última evaluación, dirigiendo así el tratamiento clínico.

La segunda, "consistencia retrospectiva", es la proporción de individuos con un diagnóstico asignado en la última evaluación que habían

recibido el mismo diagnóstico en la primera evaluación. Esto es conceptualmente similar a la sensibilidad y, al igual que con la consistencia prospectiva, los valores altos indican una buena consistencia temporal del diagnóstico. Así, si un diagnóstico realizado por un clínico en la última evaluación, cuando se dispone de más información, coincide con el diagnóstico realizado en la evaluación inicial, se podría argumentar que la presentación clínica inicial fue captada y diagnosticada adecuadamente.

Sin embargo, los índices de consistencia prospectiva y retrospectiva no tienen en cuenta el hecho de que pueden aparecer nuevos casos después de la presentación inicial y que otros casos pueden remitir (Pettit et al. 2005), lo que se corrige mediante la utilización de la tercera medida de coherencia temporal, el coeficiente kappa (Cohen 1960). El coeficiente de kappa es el acuerdo entre los diagnósticos de la primera y la última evaluación y mide el acuerdo que corrige el efecto del azar. Hemos adoptado las directrices para la interpretación de los coeficientes kappa de Altman (Altman et al. 2000): <0,20 mal acuerdo; 0,21-0,40 acuerdo justo; 0,41-0,60 acuerdo moderado; 0,61-0,80 buen acuerdo; y 0,81-1,00 muy buen acuerdo.

2. Constancia diagnóstica:

Debido a que la consistencia prospectiva y retrospectiva y el coeficiente de kappa se basan sólo en dos evaluaciones, a menudo no reflejan el proceso de diagnóstico a través de múltiples evaluaciones, que es más característico de la práctica clínica rutinaria (Baca-Garcia et al. 2007). Para capturar este proceso, también medimos la proporción de pacientes que recibieron el mismo diagnóstico en al menos el 75% de las evaluaciones. Desde una perspectiva clínica, esta medida evaluaría mejor la estabilidad de los diagnósticos a lo largo de sucesivos encuentros clínicos que la información diagnóstica obtenida en dos puntos temporales distantes (hasta 30 años en nuestro estudio). Los sujetos que recibieron diagnósticos de trastorno bipolar en al menos el 75% de las evaluaciones fueron categorizados con un trastorno bipolar estable.

5.2.2 Error diagnóstico y comorbilidad

Los temas de diagnóstico erróneo y comorbilidad se han abordado simultáneamente en el presente estudio. La comorbilidad frecuente en el trastorno bipolar (Grant et al. 2005; McElroy et al. 2001; Krishnan et al. 2005; Fogarty et al. 1994), como los trastornos de ansiedad, los trastornos de personalidad y el abuso de sustancias, añade una complicación notable a su diagnóstico preciso, y explica una gran proporción de su diagnóstico erróneo.

Cabe destacar que como consecuencia de nuestro esfuerzo por explorar los cambios diagnósticos a lo largo del tiempo, sólo se incluyeron en el estudio los diagnósticos principales. Las enfermedades comórbidas según las pautas diagnósticas deben registrarse como diagnósticos auxiliares cuando son independientes de la enfermedad primaria. La comorbilidad denota la aparición conjunta de más trastornos somáticos o psiquiátricos con diferente fisiopatología en una sola persona, ya sea simultáneamente o de forma vitalicia (Feinstein 1970). El uso de diagnósticos auxiliares en España es escaso, pero la inclusión de estos diagnósticos podría haber alterado parcialmente nuestros resultados sobre comorbilidad.

Reconociendo esta desventaja, investigamos:

- La prevalencia de los principales trastornos psiquiátricos en la muestra a partir del número total de evaluaciones.
- El flujo de cambio de diagnóstico entre los trastornos psiquiátricos y el diagnóstico del trastorno bipolar, comparando el número de diagnósticos específicos diferentes del trastorno bipolar a lo largo del período de observación.

Estos resultados, en cuanto a otros trastornos psiquiátricos, se ven sesgados por ser obtenidos en una submuestra de pacientes con al menos un diagnóstico de trastorno bipolar y selecionada de la muestra general de pacientes atendidos en los Centros de Salud Mental. En esta submuestra, de 21.674 pacientes, se han seleccionado 14.557 que habían tenido al menos 10 visitas durante el período de estudio y un mínimo de un año de seguimiento. Esto supone que estos diagnósticos fuera del trastorno bipolar son los que llevan al error diagnóstico o son comorbilidades del trastorno bipolar. Por otro lado, las frecuencias de presentación de estos diagnósticos no representan las de la población general; debido a este sesgo de selección de los pacientes.

5.2.3 Análisis estadístico

El método de Wald (Altman et al. 2000) nos sirvió para comparar las medidas de consistencia temporal de los diagnósticos de trastorno bipolar y para calcular los intervalos de confianza para cada medida de consistencia temporal (Statistical Package for the Social Sciences, versión 27.0). De manera conservadora,

consideramos que dos intervalos de confianza que comparten un límite o que no se superponen son significativamente diferentes entre sí. También se comparó la prevalencia de diferentes diagnósticos psiquiátricos entre aquellos con trastorno bipolar estable mediante pruebas de Chi-cuadrado y test exacto de Fisher. Para comparar los sujetos de la muestra con respecto a la constancia diagnóstica y el género se utilizaron pruebas de Chi-cuadrado y test exacto de Fisher. Todas estas comparaciones se realizaron en dos colas. Los análisis estadísticos se realizaron en dos pasos para buscar los determinantes de la inestabilidad: análisis univariados seguidos de un análisis multivariante mediante regresión logística. Las variables independientes significativas fueron seleccionadas e introducidas en análisis de regresión logística con estabilidad (75% de las visitas diagnosticado como tal) versus inestabilidad como variable dependiente con el método de eliminación progresiva (como criterio de ajuste del modelo se usó la razón de verosimilitud). Se incluyeron en el modelo como variables independientes: género, estado civil, nivel educativo, situación laboral, ocupación, tipo de convivencia y antecedentes de atención psiquiátrica. Esta técnica crea un modelo probabilístico que permite estimar el riesgo (mediante *odds ratio* [OR] que proporciona el modelo) que comportan los distintos valores de variables independientes sobre una variable dependiente dicotómica (existencia o no de de estabiliadad diagnóstica).

6 RESULTADOS

Resumen

Un total de 14.557 pacientes fueron diagnosticados de trastorno bipolar, durante al menos una evaluación, recibieron al menos 10 visitas y tuvieron al menos un año de seguimiento. El 63,9% eran mujeres y el 36,1% varones. Hubo un total de 2.026 pacientes que fueron diagnosticados de trastorno bipolar en su primera y última evaluación. En la primera visita se diagnosticó a 3.988 pacientes un trastorno bipolar con una consistencia prospectiva del 50,8%. En la última visita se diagnosticó a 5.396 pacientes un trastorno bipolar con una consistencia retrospectiva del 37,5%. Por otro lado, el valor de kappa fue de 0,17. Una de las causas más frecuentes de confusión en el diagnóstico del trastorno bipolar son los diversos diagnósticos en la categoría F3 de trastornos afectivos no bipolares. La constancia diagnóstica del trastorno bipolar fue del 18,6%. Los pacientes con un diagnóstico estable de trastorno bipolar se diagnosticaron antes y precisaron un menor número de evaluaciones que aquellos que tenían un diagnóstico no estable; los que tenían un diagnóstico no estable requerían menos tiempo y menos visitas para que se les retirase este diagnóstico. Teniendo en cuenta únicamente los pacientes con un diagnóstico estable bipolar, se encontró una prevalencia del 0,4%. En la regresión logística realizada se relacionó significativamente el presentar un diagnóstico de trastorno bipolar estable o no con: el estado civil, el nivel educativo, la situación laboral y los antecedentes personales de asistencia psiquiátrica.

6.1 DESCRIPCIÓN MUESTRAL

Un total de 14.557 pacientes recibieron un diagnóstico de trastorno bipolar, de acuerdo con CIE-10, durante al menos una evaluación, recibieron al menos 10 visitas y tuvieron al menos un año de seguimiento. Estos 14.557 pacientes recibieron 848.147 consultas psiquiátricas y/o psicológicas. La duración media del seguimiento de estos pacientes fue de 3.295,9 días (desviación estándar [DE] 1.967,6 días), la media de visitas fue de 58,3 (DE 66,7) y la mediana de 38 visitas.

6.2 FACTORES SOCIODEMOGRÁFICOS

De la muestra de 14.557 pacientes se recogieron los datos sociodemográficos de al menos 14.297 pacientes. El 63,9% eran mujeres (n=9.134) y el 36,1% varones (n=5.161); un paciente presentaba un género indeterminado (Tabla 5) (Figura 4).

En cuanto al estado civil, la mayoría de la muestra (51%) estaban casados (Tabla 6) (Figura 5). El 32,2% de los pacientes tenían un nivel de estudios de educación primaria, y solo el 9,2% tenía estudios superiores (titulado o licenciado) en contraposición al 12,8% que eran analfabetos o no habían cursado estudios (Tabla 7).

Un 29,6% de la muestra tenía trabajo activo, un 9,5% contaba con una incapacidad laboral (temporal o permanente), un 12% recibían una retribución (por jubilación o renta) y un 24% se dedicaba a las labores de casa (Tabla 8).

GÉNERO		Frecuencia	Porcentaje
	Mujer	9134	63,9
	Varón	5161	36,1
	Total	14295	100,0
	Perdidos	2	0,0
Total		14297	100,0

Tabla 5. Género.

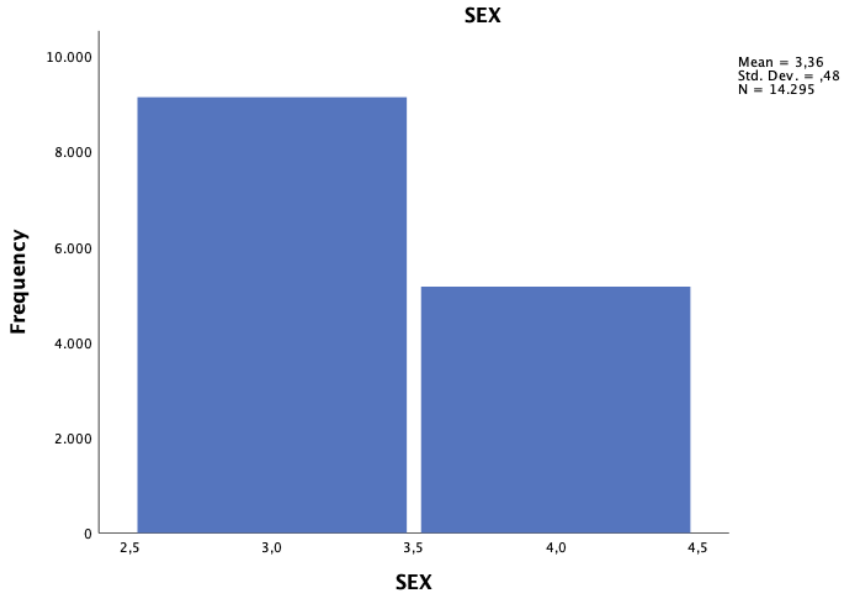

Figura 4. Género.

ESTADO CIVIL		Frecuencia	Porcentaje
	Casado	7297	51,0
	Divorciado	320	2,2
	Soltero	4873	34,1
	Viudo	834	5,8
	Separado	568	4,0
	Perdidos	405	2,8
Total		14297	100,0

Tabla 6. Estado civil.

NIVEL EDUCATIVO		Frecuencia	Porcentaje
	Analfabeto	365	2,6
	Sin estudios	1458	10,2
	Primaria	4646	32,5
	Graduado escolar	2505	17,5
	Bachillerato	2110	14,8
	COU	812	5,7
	Titulado	925	6,5
	Licenciado	389	2,7
	Otros	161	1,1
	Perdidos	926	6,5
Total		14297	100,0

Tabla 7. Nivel educativo.
COU: Curso de Orientación Universitaria.

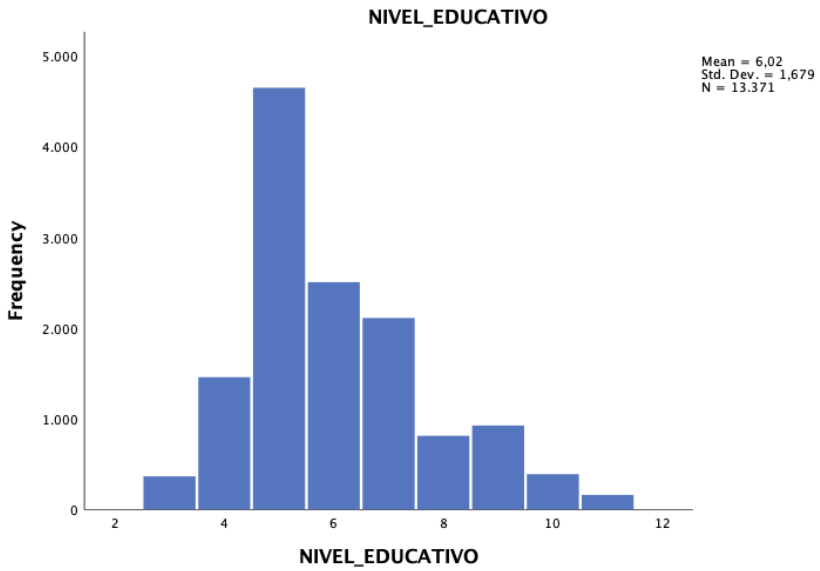

Figura 5. Nivel educativo.
3: Analfabeto. **4:** Sin estudios. **5:** Primaria. **6:** Graduado escolar. **7:** Bachillerato . **8:** COU (Curso de Orientación Universitaria). 9: Titulado. **10:** Licenciado. **11:** Otros.

SITUACIÓN LABORAL	Frecuencia	Porcentaje
Servicio militar	18	0,1
ILT	1091	7,6
ILP	271	1,9
En activo	4228	29,6
Buscando primer empleo	197	1,4
Paro con subsidio	411	2,9
Paro sin subsidio	820	5,7
Jubilación	1676	11,7
Rentista	40	0,3
Estudiando	769	5,4
Labores de casa	3427	24,0
Perdidos	1349	9,4
Total	14297	100,0

Tabla 8. Situación laboral.
ILT: Incapacidad Laboral Temporal. **ILP:** Incapacidad Laboral Permanente.

En la Tabla 9 se recogen los datos de ocupación, donde la categoría mayormente representada es "sin trabajo" con un 31,8% (n=4.549). El tipo de convivencia más frecuente es con el cónyuge el 48,8% (n=6.980), seguido de con familiares 17,6% (2.518). Es de destacar que un 8,5% de los pacientes viven solos (n=1.216) (Tabla 10). También se recoge el ámbito donde se realiza el diagnóstico de trastorno bipolar, o si no tiene antecedentes previos de asistencia psiquiátrica, antes de la primera evaluación en el Centro de Salud Mental de la Comunidad de Madrid (Tabla 11).

OCUPACIÓN	Frecuencia	Porcentaje
Sin trabajo	4549	31,8
Profesionales y técnicos	1258	8,8
Directivo	120	,8
Administrativo	1116	7,8
Comerciales	456	3,2
Hosteleria y servicios seguridad	1385	9,7
Agricultura	124	0,9
Industria construcción	763	5,3
Otros	4462	31,2
Fuerzas armadas	63	0,4
Perdidos	1	0,0
Total	14297	100,0

Tabla 9. Ocupación.

TIPO DE CONVIVENCIA	Frecuencia	Porcentaje
Otros	586	4,1
Solo	1216	8,5
Conyuge	6980	48,8
Pareja	450	3,1
Familiares	2518	17,6
Solo padre	125	0,9
Solo madre	673	4,7
Hijos	927	6,5
Otros familiares	506	3,5
Institucionalizado	186	1,3
Perdidos	130	0,9
Total	14297	100,0

Tabla 10. Tipo de convivencia.

ANTECEDENTES	Frecuencia	Porcentaje
Diagnóstico ambulatorio	3358	23,5
Diagnóstico hospitalario	2028	14,2
Sin antecedentes	3065	21,5
Perdidos	5846	40,8
Total	14297	100,0

Tabla 11. Antecedentes de asistencia psiquiátrica.

Durante los 30 años de duración de recogida de datos del estudio, los pacientes tienen un tiempo de seguimiento variable de alrededor de 9 años, con una media de 3.295,9 días (DE 1.967,6 días). La edad de los pacientes al inicio de su seguimiento fue de 44,1 años (DE 16,05 años) y al final del seguimiento fue de 53,6 años (DE 16,05 años). La distribución por edades puede verse en el gráfico de edad al inicio (Figura 6) del seguimiento en el Centro de Salud Mental. En esta muestra se puede observar que hay pacientes no adultos, esto se debe a un inicio del seguimiento en edades infantiles o juveniles y que se ha realizado el diagnóstco de trastorno bipolar en la edad adulta.

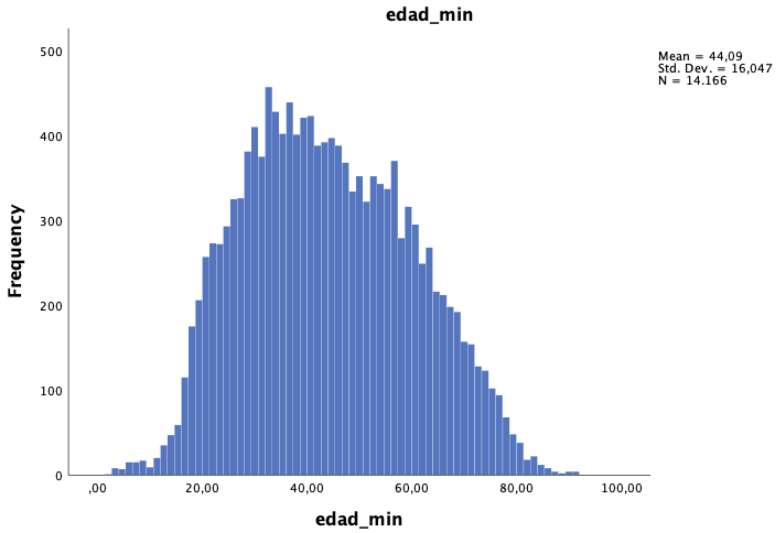

Figura 6. Edad al inicio del seguimiento.

6.2.1 Diagnósticos Psiquiátricos

Se ha realizado una comparativa de los 3.988 pacientes que fueron diagnosticados de trastorno bipolar en la primera evaluación (27,4% del total) con los diagnósticos agrupados en códigos Fx de la CIE-10 en la evaluación final de cada paciente, que suman un total de 5.396 diagnósticos finales (37,1% del total). Se considera una concordancia baja del 0-25%, media del 26-50%, alta 51-75% y muy alta del 76-100%.

Se compararon los diagnósticos agrupados en códigos Fx de la CIE-10 en la evaluación inicial (15.082 diagnósticos) con los diagnósticos agrupados en códigos Fx de la CIE-10 en la evaluación final (15.507 diagnósticos). En este caso la mayor concordancia entre diagnósticos iniciales y finales se encuentra en la categoría F3 final; esto se debe a que la muestra está seleccionada de pacientes que han sido diagnosticados al menos una vez de trastorno bipolar. De los pacientes que tuvieron un diagnostico en F3 (Trastornos del humor [afectivos]) en la primera evaluación (n=8.141) un 77,77% (6.331 diagnósticos) recibe un diagnostico final en el mismo epígrafe F3. El resto de las categorías Fx presentaron unas concordancias altas (F0, F4, F5, F6, F8, F9) o medias (F1, F2, F7) con diagnósticos finales F3. Hay que reseñar una concordancia alta en los pacientes que tuvieron un diagnostico en F2 (Esquizofrenia, trastornos esquizotípicos y trastornos delirantes), que incluye los diagnósticos F20-F29, en la primera evaluación (n=1.937) un 60,04% (1.163 diagnósticos) de los pacientes recibe un diagnostico final en el mismo epígrafe F2. También se ha encontrado una concordancia media en los pacientes que tuvieron un diagnostico en F1 (Trastornos mentales y del comportamiento debidos al uso de sustancias psicoactivas), que incluye los diagnósticos F10-F19, en la primera evaluación (n=439) un 30,52% (134 diagnósticos) recibe un diagnostico final en el mismo epígrafe F1. (Tabla12) (Figura 7).

Un 77,53% de los pacientes diagnosticados de trastorno bipolar en la primera evalución (n=3.092 pacientes) recibieron, en su evaluación final, un diagnostico correspondiente al epígrafe F3 (Trastornos del humor [afectivos]) de la CIE-10, que incluye los diagnósticos F30-F39 (Tabla 13) (Figura 8).

	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
F0 n= 143	34 (7%)	2 (1,40%)	18 (12,59%)	85 (59,44%)	14 (9,79%)	0 (0%)	6 (4,20%)	0 (0%)	0 (0%)	0 (0%)
F1 n= 439	7 (1,59%)	134 (30,52%)	92 (20,96%)	211 (48,06%)	35 (7,97%)	1 (0,23%)	29 (6,61%)	0 (0%)	0 (0%)	0 (0%)
F2 n= 1937	20 (1,03%)	33 (1,70%)	1163 (60,04%)	686 (35,42%)	76 (3,92%)	8 (0,41%)	56 (2,89%)	8 (0,41%)	1 (0,05%)	2 (0,10%)
F3 n= 8141	176 (2,16%)	124 (1,52%)	568 (6,98%)	6331 (77,77%)	936 (11,50%)	37 (0,45%)	390 (4,79%)	36 (0,44%)	1 (0,01%)	16 (0,20%)
F4 n= 3435	63 (1,83%)	76 (2,21%)	272 (7,92%)	2168 (63,11%)	820 (23,87%)	17 (0,49%)	247 (7,19%)	14 (0,41%)	1 (0,03%)	14 (0,41%)
F5 n=138	2 (1,45%)	3 (2,17%)	7 (5,07%)	80 (57,97%)	18 (13,04%)	25 (18,12%	18 (13,04%)	0 (0%)	1 (0,72%)	1 (0,72%)
F6 n= 606	8 (1,32%)	16 (2,64%)	95 (15,68%)	343 (56,60%)	73 (12,05%)	4 (0,66%)	156 (25,04%)	4 (0,66%)	0 (0%)	1 (0,17%)
F7 n= 75	1 (1,33%)	0 (0%)	17 (22,67%)	34 (45,33%)	6 (8,00%)	0 (0%)	5 (6,67%)	32 (42,67%)	0 (0%)	1 (1,33%)
F8 n= 38	1 (2,63%)	3 (7,89%)	4 (10,53%)	27 (71,05%)	4 (10,53%)	1 (2,63%)	1 (2,63%)	0 (0%)	1 (2,63%)	0 (0%)
F9 n= 130	1 (0,77%)	3 (2,31%)	19 (14,62%)	68 (52,31%)	18 (13,85%)	2 (1,54%)	24 (18,56%)	3 (2,31%)	2 (1,54%)	10 (7,69%)

Tabla 12. Diagnósticos finales agrupados en categorías Fx de los pacientes diagnosticados en la primera evaluación en categorías Fx.
En verde: diagnósticos iniciales.
En rojo: diagnósticos finales.
El grado de concordancia se realiza de acuerdo a:

Concordancia muy alta	76-100%
Concordancia alta	51-75%
Concordancia media	26-50%
Concordancia baja	0-25%

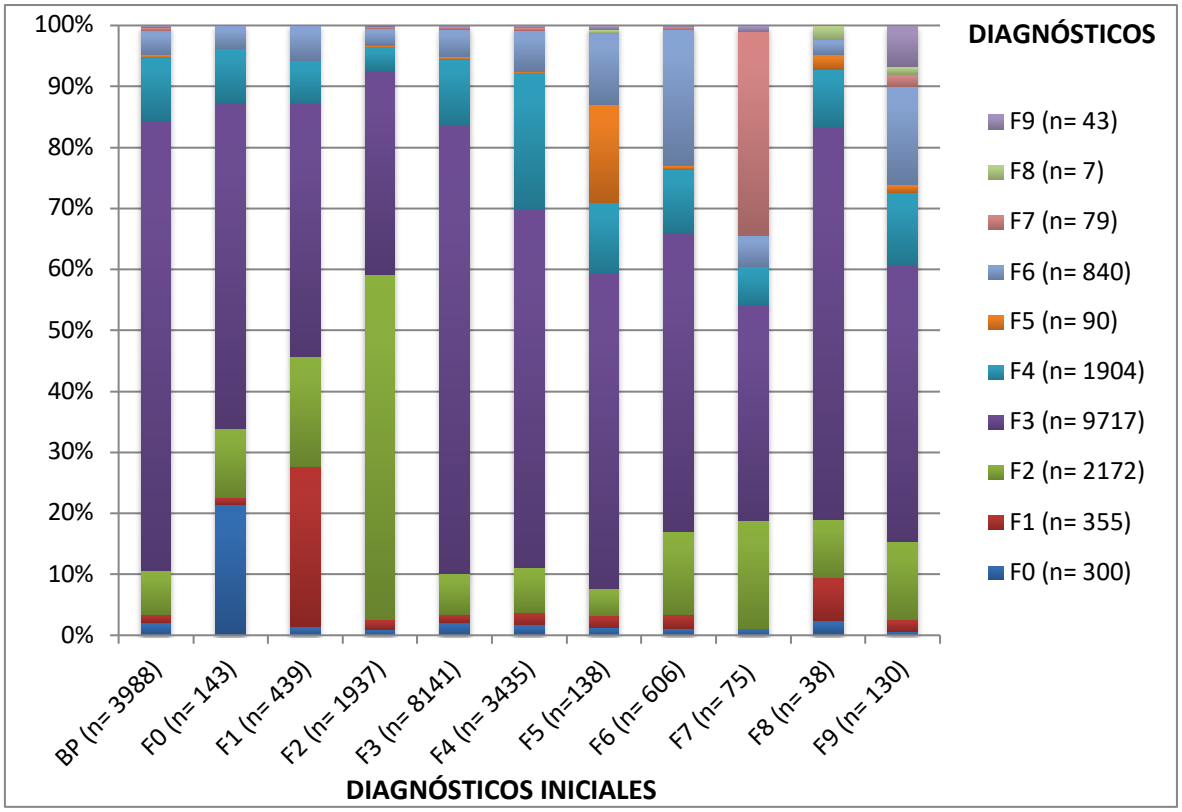

Figura 7. Diagnósticos finales agrupados en categorías Fx de los pacientes diagnosticados en la primera evaluación de trastorno bipolar y en categorías Fx.
BP: trastorno bipolar.

	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
TB n= 3988	85 (2,13%)	61 (1,53%)	301 (7,55%)	3092 (77,53%)	429 (10,76%)	19 (0,48%)	167 (4,19%)	22 (0,55%)	1 (0.03%)	12 (0,30%)

Tabla 13. Diagnósticos finales agrupados en categorías Fx de los pacientes diagnosticados en la primera evaluación de trastorno bipolar.
TB: trastorno bipolar.
El grado de concordancia se realiza de acuerdo a:

Concordancia muy alta	76-100%
Concordancia alta	51-75%
Concordancia media	26-50%
Concordancia baja	0-25%

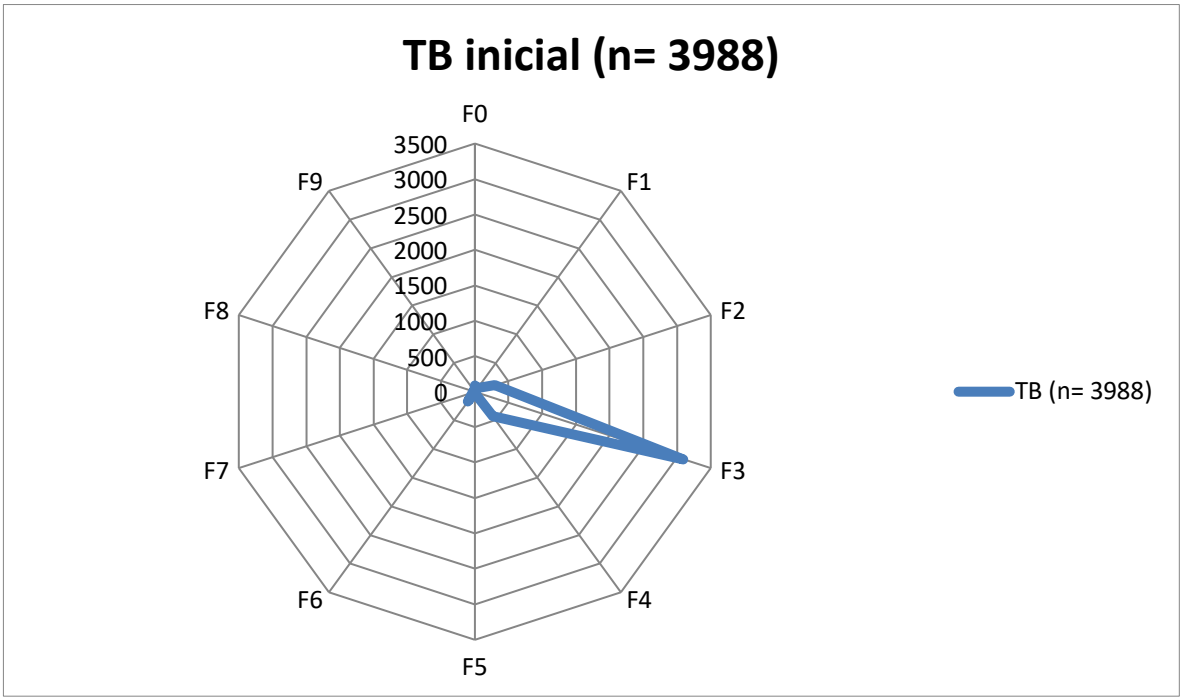

Figura 8. Diagnósticos finales agrupados en categorías Fx de los pacientes diagnosticados en la primera evaluación de trastorno bipolar.
TB: trastorno bipolar.

Al igual que se realizó con los diagnósticos iniciales, también se compararon los diagnósticos agrupados en códigos Fx de la CIE-10 en la evaluación final (15.507 diagnósticos) con los diagnósticos agrupados en códigos Fx de la CIE-10 en la evaluación inicial (15.082 diagnósticos). En este caso la mayor concordancia entre diagnósticos iniciales y finales se encuentra en la categoría F3 final; esto se debe, al igual que se decía antes, a que la muestra está seleccionada de pacientes que han sido diagnosticados al menos una vez de trastorno bipolar. De los pacientes que tuvieron un diagnostico en F3 (Trastornos del humor [afectivos]) en la última evaluación (n=9.717) un 65,15% (6.331 diagnósticos) recibieron un diagnóstico final en el mismo epígrafe F3 al inicio. En el resto de las categorías Fx, únicamente se presentó una concordancia alta en F0 (Trastornos mentales orgánicos, incluidos los trastornos sintomáticos) con un 58,66% (176 diagnósticos). Se obtuvieron unas concordancias medias en F1, F2, F4, F5, F6, F7, F9; y baja en F8. Es destacable una concordancia alta en los pacientes que tuvieron un diagnostico inicial en F2 (Esquizofrenia, trastornos esquizotípicos y trastornos delirantes), con un 53,54% (1.163 diagnósticos) con su propia categoría final F2. Para los epígrafes F1, F4, F5 y F7 se hallaron unas concordancias medias; y el resto de cruces entre categorías mostró una concordancia baja. (Tabla 14) (Figura 9).

Un 63,73% de los pacientes diagnosticados de trastorno bipolar en la última evalución (n=5.396 pacientes) recibieron, en su evaluación inicial, un diagnostico correspondiente al epígrafe F3 (Trastornos del humor [afectivos]) de la CIE-10, que incluye los diagnósticos F30-F39 (Tabla 15) (Figura 10).

	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
F0 n= 300	34 (11,33%)	7 (0,23%)	20 (6,66%)	176 (58,66%)	63 (21%)	2 (0,66%)	8 (2,66%)	1 (0,33%)	1 (0,33%)	1 (0,33%)
F1 n= 355	2 (0,56%)	134 (37,74%)	33 (9,29%)	124 (34,92%)	76 (21,40%)	3 (0,84%)	16 (4,50%)	0 (0%)	3 (0,84%)	3 (0,84%)
F2 n= 2172	18 (0,82%)	92 (4,23%)	1163 (53,54%)	568 (26,15%)	272 (12,52%)	7 (0,32%)	95 (4,37%)	17 (0,78%)	4 (0,18%)	19 (0,87%)
F3 n= 9717	85 (0,87%)	211 (2,17%)	686 (7,05%)	6331 (65,15%)	2168 (22,31%)	80 (0,82%)	343 (3,52%)	34 (0,34%)	27 (0,27%)	68 (0,69%)
F4 n= 1904	14 (0,73%)	35 (1,83%)	76 (3,99%)	936 (49,15%)	820 (43,06%)	18 (0,94%)	73 (3,83%)	6 (0,31%)	4 (0,21%)	18 (0,94%)
F5 n=90	0 (0%)	1 (1,11%)	8 (8,88%)	37 (41,11%)	17 (18,88%)	25 (27,77%)	4 (4,44%)	0 (0%)	1 (0,11%)	2 (2,22%)
F6 n= 840	6 (0,71%)	29 (3,45%)	56 (6,66%)	390 (46,42%)	247 (29,40%)	18 (2,14%)	156 (18,57%)	5 (0,59%)	1 (0,11%)	24 (2,85%)
F7 n= 79	0 (0%)	0 (0%)	8 (10,12%)	36 (45,56%)	14 (17,72%)	0 (0%)	4 (5,06%)	32 (40,50%)	0 (0%)	3 (3,79%)
F8 n= 7	0 (0%)	0 (0%)	1 (14,28%)	1 (14,28%)	1 (14,28%)	1 (14,28%)	0 (0%)	0 (0%)	1 (14,28%	2 (28,57%)
F9 n= 43	0 (0%)	0 (0%)	2 (4,65%)	16 (37,20%)	14 (32,55%)	1 (2,32%)	1 (2,32%)	1 (2,32%)	0 (0%)	10 (23,25%)

Tabla 14. Diagnósticos iniciales agrupados en categorías Fx de los pacientes diagnosticados en la última evaluación en categorías Fx.
En verde: diagnósticos iniciales.
En rojo: diagnósticos finales.
El grado de concordancia se realiza de acuerdo a:

Concordancia muy alta	76-100%
Concordancia alta	51-75%
Concordancia media	26-50%
Concordancia baja	0-25%

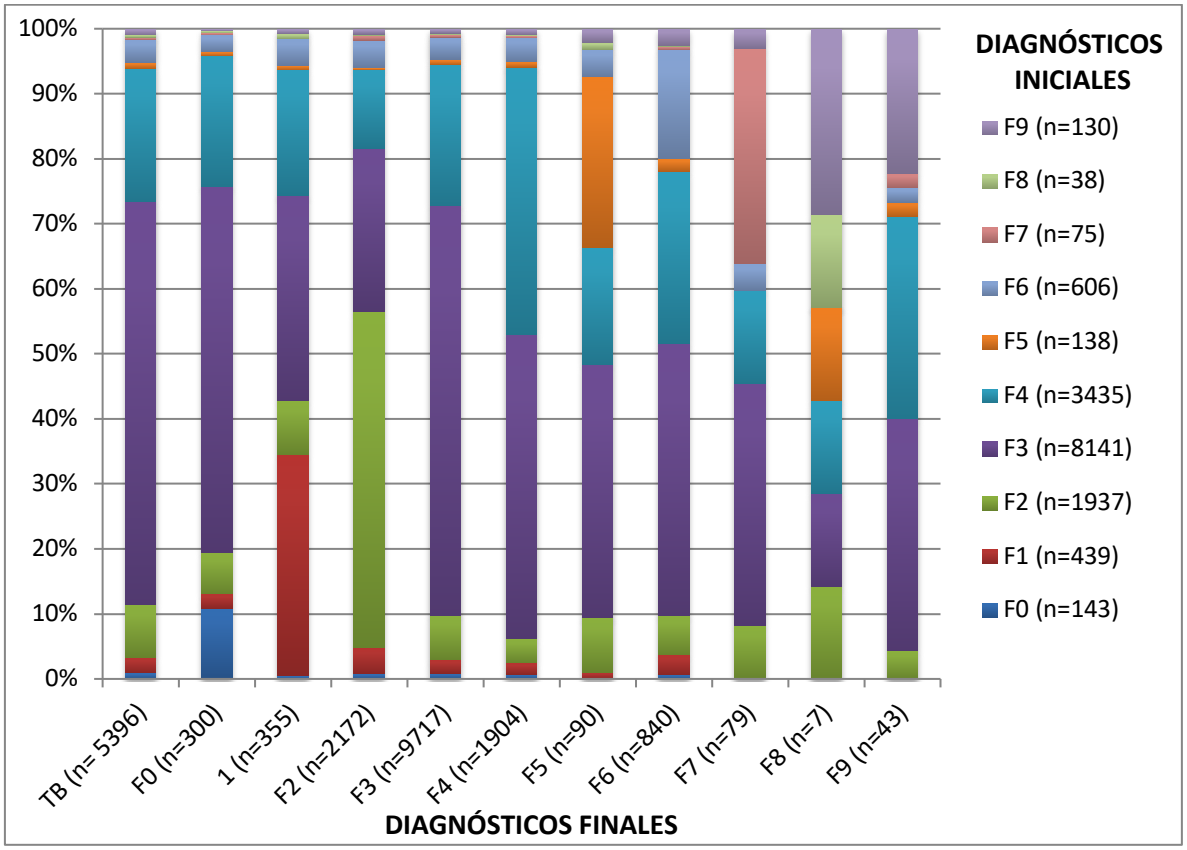

Figura 9. Diagnósticos iniciales agrupados en categorías Fx de los pacientes diagnosticados en la última evaluación de trastorno bipolar y en categorías Fx.
TB: trastorno bipolar.

	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
TB (n= 5396)	51 (0,94%)	136 (2,52%)	449 (8,32%)	3439 (63,73%)	1135 (21,03%)	51 (0,94%)	195 (3,61%)	21 (0,38%)	19 (0,35%)	53 (0,35%)

Tabla 15. Diagnósticos iniciales agrupados en categorías Fx de los pacientes diagnosticados en la última evaluación de trastorno bipolar.
TB: trastorno bipolar.
El grado de concordancia se realiza de acuerdo a:

Concordancia muy alta	76-100%
Concordancia alta	51-75%
Concordancia media	26-50%
Concordancia baja	0-25%

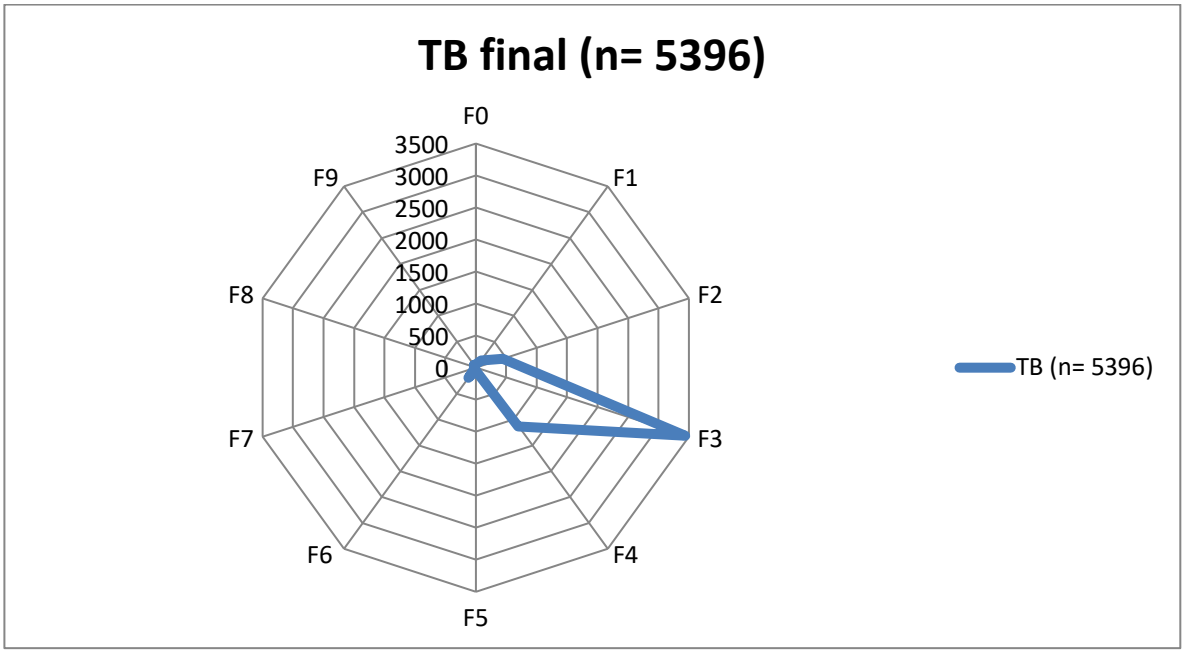

Figura 10. Diagnósticos iniciales agrupados en categorías Fx de los pacientes diagnosticados en la última evaluación de trastorno bipolar.
TB: trastorno bipolar.

6.3 CONSISTENCIA TEMPORAL DEL DIAGNÓSTICO DE TRASTORNO BIPOLAR

Hubo un total de 2.026 pacientes que fueron diagnosticados de trastorno bipolar en su primera y última evaluación. En la primera visita se diagnosticó a 3.988 pacientes un trastorno bipolar con una consistencia prospectiva del 50,8%. En la última visita se diagnosticó a 5.396 pacientes un trastorno bipolar con una consistencia retrospectiva del 37,5% (Tablas 16 y 17). Por otro lado, el valor de kappa fue bajo entre el primer y el último diagnóstico, kappa=0,17 (Tabla 17).

		TB final		Total
		NO	SI	
TB inicial	NO	7199	3370	10569
	SI	1962	2026	3988
Total		9161	5396	14557

Tabla 16. Pacientes con diagnósticos de trastorno bipolar iniciales y finales.
TB: trastorno bipolar.

	Valores	Intervalo de confianza (95%)
Primer diagnostico de TB[1]	3.988	
Consistencia prospectiva	50,8%	49,48-52,12
Último diagnostico de TB[1]	5.396	
Consistencia retrospectiva	37,5%	36,52-38,57
Kappa[2]	17,0	15,4-18,5

Tabla 17. Consistencia temporal para el diagnostico de trastorno bipolar con criterios CIE-10.
[1]**TB:** trastorno bipolar
[2]Kappa (κ), significación estadística (p<0,001).

6.4 ERRORES DIAGNÓSTICOS CON EL TRASTORNO BIPOLAR

Durante el seguimiento se encontró una gran variabilidad en las categorías diagnósticas. Hay unas categorías que especialmente podrían causar confusión en el diagnóstico del trastorno bipolar (Tabla 18).

Los diagnósticos de la categoría F4 (Trastornos neuróticos, trastornos relacionados con el estrés y trastornos somatomorfos) aparecieron en la primera evaluación en el 21,03% (n=1.135) de los pacientes que eran diagnosticados de trastorno bipolar en la última visita. De forma inversa, el 10,76% (n=429) de los pacientes diagnosticados al inicio de trastorno bipolar acababan finalmente con un diagnóstico de la categoría F4.

Otra categoría que conducía al error diagnóstico es la F2 (Esquizofrenia, trastornos esquizotípicos y trastornos delirantes), que aparerecían al inicio en un 8,32% (n=449) de los pacientes diagnosticados de trastorno bipolar al final; y en un 7,55% (n=301) de los casos como diagnóstico final de aquellos que fueron diagnosticados de trastorno bipolar al principio.

En menor medida, los diagnósticos de la categoría F6 (Trastornos de la personalidad y del comportamiento en adultos) se recogían al inicio en un 3,61% (n=195) de los trastornos bipolares finales y, en la última evaluación ascendían al 4,19% (n=167) de los diagnosticados inicialmente como trastornos bipolares.

En el resto de categorías, los porcentajes diagnósticos fueron inferiores al 3% tanto para categorías diagnósticas iniciales como finales.

	TB final	TB inicial
F20-F29	449 (8,32%)	301 (7,55%)
F40-F49	1135 (21,03%)	429 (10,76%)
F60-F69	195 (3,61%)	167 (4,19%)

Tabla 18. Errores diagnósticos más frecuentes con trastono bipolar.
TB: trastorno bipolar.

Una de las causas más frecuentes de confusión en el diagnóstico del trastorno bipolar, como se ha visto anteriormente, son los diversos diagnósticos en la categoría F3 (Trastornos del humor [afectivos]), es decir, los trastornos afectivos no bipolares. En la evaluación inicial, 8.141 pacientes recibieron un diagnóstico pertenenciente a la categoría F3. De éstos, 3.988 pacientes presentaron un diagnóstico bipolar y 4.153 (51,0%) otro diagnóstico no bipolar dentro de la categoría F3. En la evaluación final, a 9.717 pacientes se les asignaron un diagnóstico F3, de los que 5.396 eran bipolares y 4.321 (44,5%) tenían un diagnóstico F3 no bipolar.

6.5 CONSTANCIA DIAGNÓSTICA DEL TRASTORNO BIPOLAR

La distribución del porcentaje de estabilidad diagnóstica de trastorno bipolar a lo largo del seguimiento se puede ver en la Figura 11. De la muestra total de 14.557 pacientes que fueron diagnosticados al menos en una ocasión como trastorno bipolar, con seguimiento de al menos un año y 10 consultas por facultativos, se encuentra que sólo el 18,6% (n = 2.718/14.557) confirmó el diagnóstico en el 75% de las evaluaciones (Figura 12).

De los 3.988 pacientes diagnósticados al inicio de trastorno bipolar, 2.016 lo mantuvieron

estable en al menos el 75% de las evaluaciones durante el periodo de seguimiento, lo que supone un 50,5% de los casos (n = 2.016/3.988; IC 95%: 49,22-50,77). Se encontró que 702 pacientes con diagnóstico estable de trastorno bipolar no fueron diagnosticados en la primera evaluación y constituirían un error inicial del 25,8%, (n = 702/2.718; IC 95%: 24,34-27,31). En la primera consulta 1.972 pacientes que se diagnosticaron de trastorno bipolar obtuvieron posteriormente al menos un 25% de diagnósticos diferentes y podrían ser considerados como sobrediagnóstico inicial o falsos positivos (FP), lo que corresponde al 49,4% del diagnóstico inicial (n = 1.972/3.988; IC95%: 48,12-50,77) (Tabla 19).

En la última evaluación, el número de diagnósticos de trastorno bipolar aumentó considerablemente; 2.299 de los 5.396 pacientes con diagnóstico bipolar en la última consulta se corresponden con diagnósticos estables a lo largo del seguimiento, un 42,6% (n = 2.299/5.396; IC 95%: 41,55-43,65). Sin embargo, 3.097 pacientes, un 57,4% (n = 3.097/5.396; IC95%: 56,34-58,44) de los pacientes diagnosticados finalmente como trastorno bipolar en esta última visita no mantuvieron los criterios de estabilidad en su evolución y pudieron ser considerados como sobrediagnóstico final (FP). Por último, 419 pacientes no diagnosticados en esta evaluación constituirían un error diagnóstico final del 15,4% (n = 419/2.718; IC95%: 14,19-16,64) (Tabla 20).

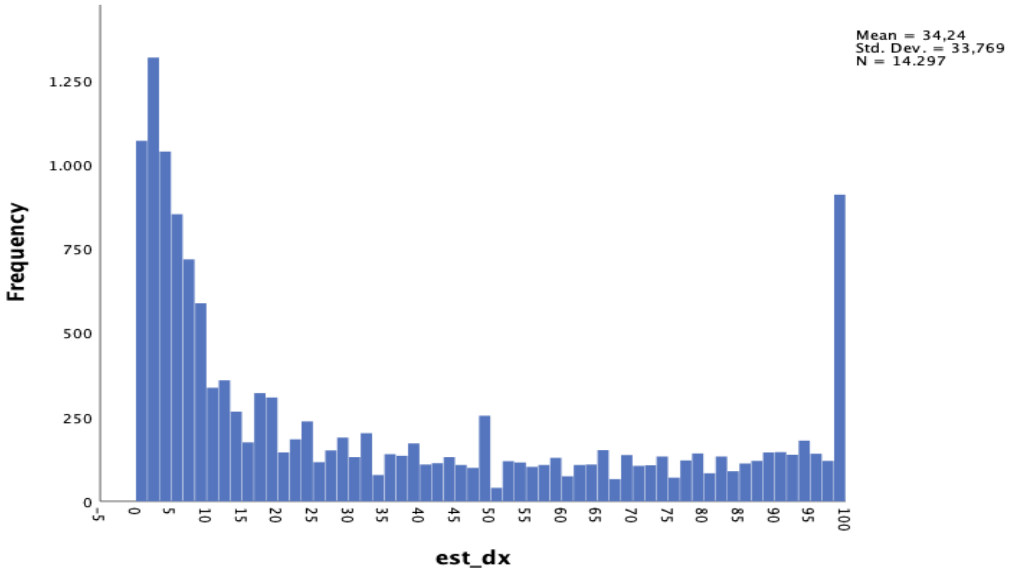

Figura 11. Porcentajes de estabilidad diagnóstica bipolar durante el seguimiento.

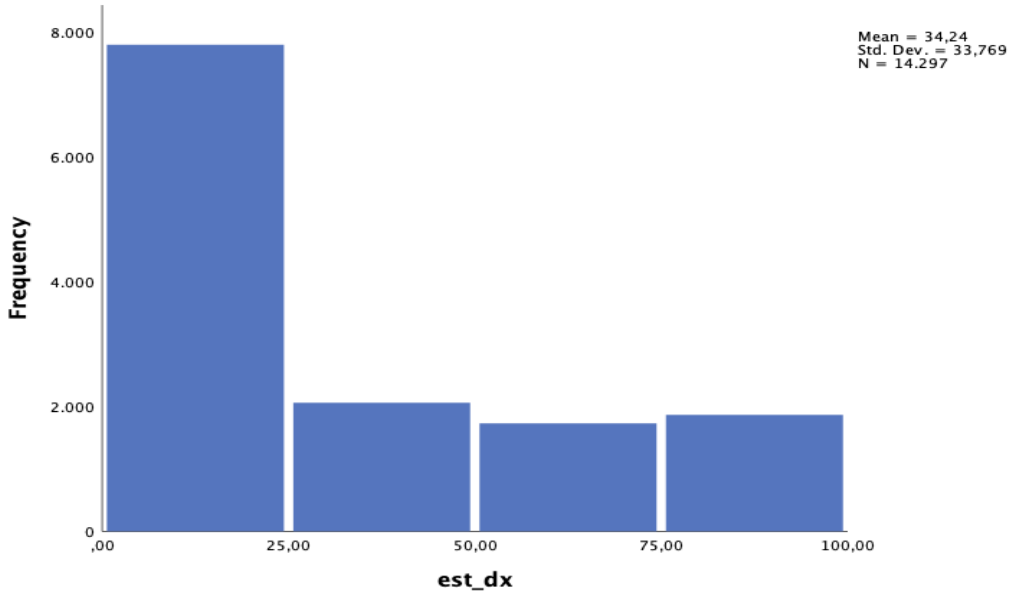

Figura 12. Porcentajes de diagnóstico estable de trastorno bipolar.

		TB estable		
		NO	SI	Total
TB inicial	NO	9867	702	10569
	SI	1972	2016	3988
	Total	11839	2718	14557

Tabla 19. Diagnóstico estable de trastorno bipolar en la evaluación inicial.
TB: trastorno bipolar.

		TB estable		
		NO	SI	Total
TB final	NO	8742	419	9161
	SI	3097	2299	5396
	Total	11839	2718	14557

Tabla 20. Diagnóstico estable de trastorno bipolar en la evaluación final.
TB: trastorno bipolar.

La figura 13 muestra la diferencia entre la primera y la última evaluación, el número de pacientes "estables" (con más del 75% de las evaluaciones con diagnóstico de trastorno bipolar) y la existencia de errores de diagnóstico en estas evaluaciones. El "sobrediagnóstico inicial" se presenta como el exceso de diagnóstico de trastorno bipolar que se dio a los pacientes en la primera evluación y que resultaron ser "no estables" durante el período de estudio. El "error inicial" representa el número adicional de pacientes "estables" que deberían haber sido diagnosticados en la primera consulta y que no lo fueron. El "sobrediagnóstico final" son los pacientes a los que se les diagnosticó trastorno bipolar en su última consulta y que no alcanzaron

el criterio de "estabilidad". El "error final" muestra la diferencia entre los pacientes "estables" que confirmaron su diagnóstico en la última consulta y el número total de pacientes "estables" a lo largo del estudio (n=2.718).

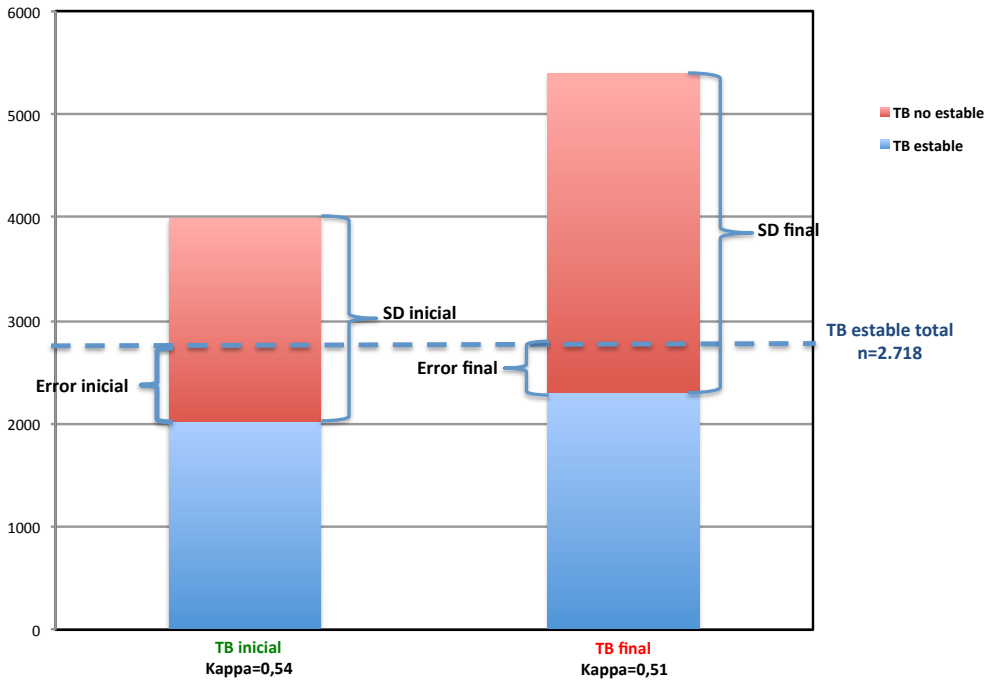

Figura 13. Comparación entre el diagnóstico del trastorno bipolar estable en primera y última consulta.
La línea discontínua azul representa el número de pacientes con al menos un 75% de diagnóstico de trastorno bipolar durante el seguimiento.
TB: trastorno bipolar.
SD: sobrediagnóstico.

6.6 ESTABILIDAD DIAGNÓSTICA RELACIONADA CON EL TIEMPO DE SEGUIMIENTO

Entre estos 2.718 pacientes bipolares "estables", el tiempo medio desde el primer contacto terapéutico dentro del sistema de Centros de Salud Mental hasta la primera vez que el paciente fue diagnosticado de trastorno bipolar fue de 318,1 días (IC95%: 188,5-347,8). La mediana fue de 0. Entre los 11.839 pacientes bipolares "no estables", el tiempo medio desde el primer contacto de seguimiento en el sistema de servicios de salud mental hasta la primera vez que el paciente fue diagnosticado de trastorno bipolar fue de 1.511,2 días (IC95%: 1.482,3-1.540,2). La mediana fue de 966 días (IC95%: 925,2-1006,7) (Figura 14). Se observa una diferencia entre el tiempo necesario para realizar el primer diagnóstico de trastorno bipolar entre aquellos que van a tener un diagnóstico estable y aquellos que no lo van a tener a lo largo de su evolución (test de Mantel-Cox, chi-cuadrado=2.852,10; p<0,0001).

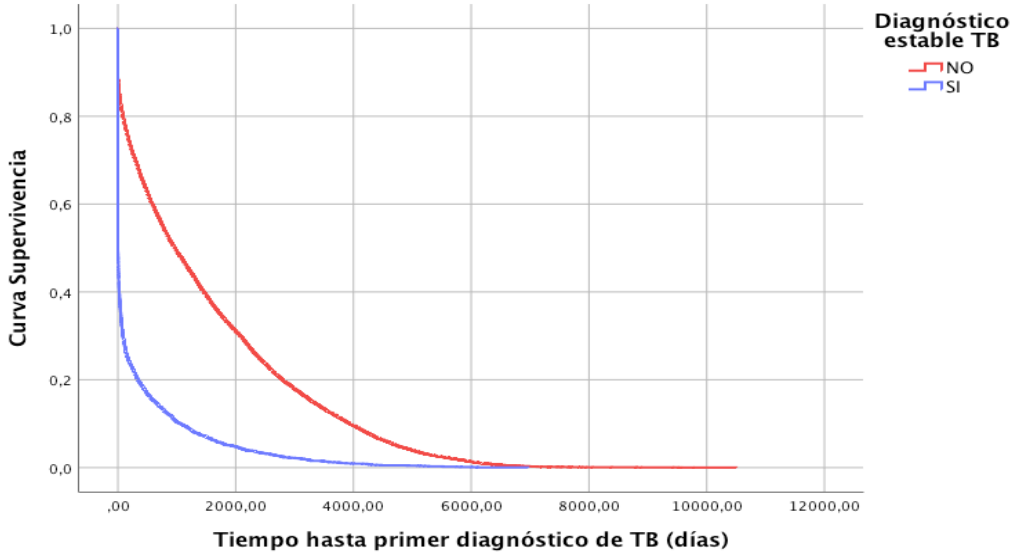

Figura 14. Tiempo hasta que se realiza el primer diagnóstico de trastorno bipolar.
La línea azul corresponde a la muestra de pacientes con diagnóstico de trastorno bipolar estable, la roja a pacientes con diagnóstico de trastorno bipolar no estable.
TB: trastono bipolar.

Entre los 2.718 pacientes bipolares "estables", el tiempo medio desde el primer contacto terapéutico dentro del sistema de servicios de salud mental hasta la última vez que el paciente fue diagnosticado de trastorno bipolar fue de 7.386,7 días. La mediana fue de 7.429 días (IC95%: 7.068,2-7.705,2). Entre los 11.839 pacientes bipolares "no estables", el tiempo medio desde el primer contacto de seguimiento en los Centros de Salud Mental hasta la última vez que el paciente fue diagnosticado de trastorno bipolar fue de 2.929,9 días (IC95%: 12.875,1-2.984,8). La mediana fue de 2.444 días (IC95%: 2.375,0-2.512,9) (Figura 15). Se observa una diferencia entre el tiempo necesario hasta que se realiza el último diagnóstico de trastorno bipolar entre aquellos que tienen un diagnóstico estable y aquellos que no (test de Mantel-Cox, chi-cuadrado=1.399,66; p<0,0001).

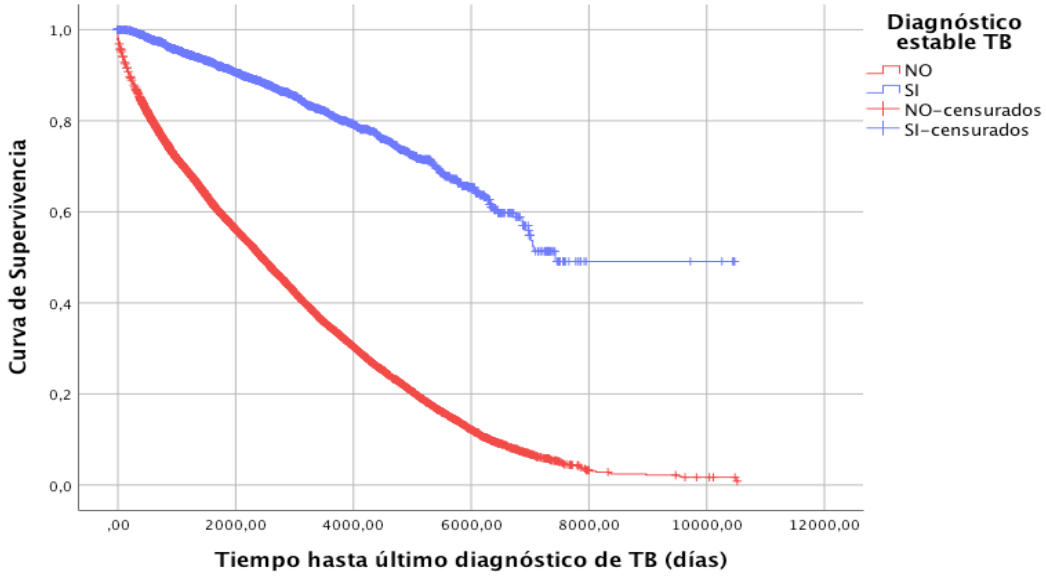

Figura 15. Tiempo hasta que se realiza el último diagnóstico de trastorno bipolar.
La línea azul corresponde a la muestra de pacientes con diagnóstico de trastorno bipolar estable, la roja a pacientes con diagnóstico de trastorno bipolar no estable.
TB: trastono bipolar.

6.7 ESTABILIDAD DIAGNÓSTICA RELACIONADA CON EL NÚMERO DE EVALUACIONES

Entre los 2.718 pacientes bipolares con diagnóstico estable, el número de visitas ambulatorias medio desde el primer contacto terapéutico dentro del sistema de servicios de salud mental hasta la primera vez que el paciente fue diagnosticado de trastorno bipolar fue de 3,7 visitas (IC95%: 3,3-4,0). La mediana fue de 1. Entre los 11.839 pacientes bipolares "no estables", el número de visitas ambulatorias medio desde el primer contacto de seguimiento en el sistema de servicios de salud mental hasta la primera vez que el paciente fue diagnosticado de trastorno bipolar fue de 21,2 visitas (IC95%: 20,5-21,9). La mediana fue de 9 visitas (IC95%: 8,6-9,3) (Figura 16). Se observa una diferencia entre el número de visitas necesario para realizar el primer diagnóstico de trastorno bipolar entre aquellos que van a tener un diagnóstico estable y aquellos que no lo van a tener a lo largo de su evolución (test de Mantel-Cox, chi-cuadrado=2.754,72; p<0,0001).

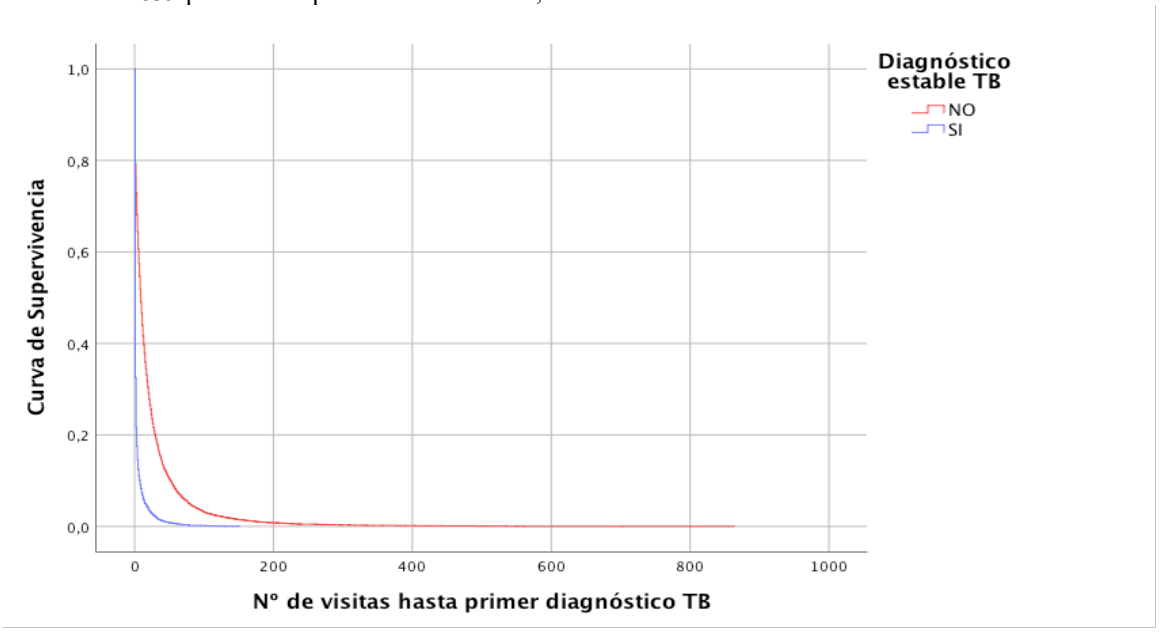

Figura 16. Nº de visitas hasta que se realiza el primer diagnóstico de trastorno bipolar.
La línea azul corresponde a la muestra de pacientes con diagnóstico de trastorno bipolar estable, la roja a pacientes con diagnóstico de trastorno bipolar no estable.
TB: trastono bipolar.

Entre los 2.718 pacientes bipolares "estables", el número de visitas ambulatorias medio desde el primer contacto terapéutico dentro del sistema de servicios de salud mental hasta la última vez que el paciente fue diagnosticado de trastorno bipolar fue de 279,1 visitas (IC95%: 243,5-314,7). La mediana fue de 186 visitas (IC95%: 152,9-219,0). Entre los 11.839 pacientes bipolares "no estables", el número de visitas ambulatorias medio desde el primer contacto de seguimiento en el sistema de servicios de salud mental hasta la última vez que el paciente fue diagnosticado de trastorno bipolar fue de 55,0 visitas (IC95%: 53,2-56,8). La mediana fue de 31 visitas (IC95%: 30,1-31,8) (Figura 17). Se observa una diferencia entre el número de evaluaciones necesario hasta que se realiza el último diagnóstico de trastorno bipolar entre aquellos que tienen un diagnóstico estable y aquellos que no (test de Mantel-Cox, chi-cuadrado=1.654,12; p<0,0001).

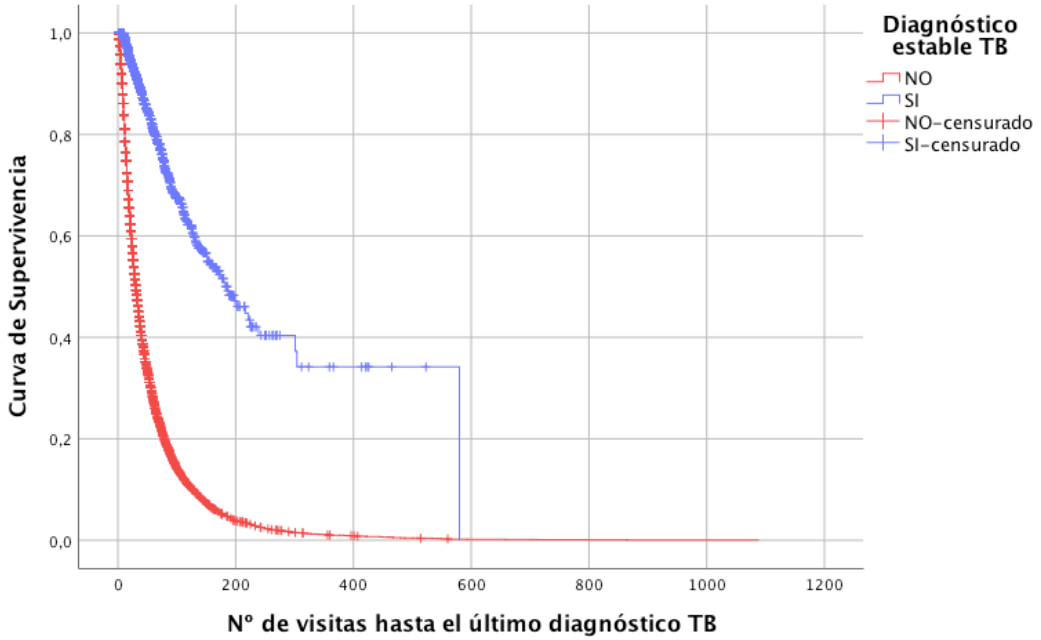

Figura 17. Nº de visitas hasta que se realiza el último diagnóstico de trastorno bipolar.
La línea azul corresponde a la muestra de pacientes con diagnóstico de trastorno bipolar estable, la roja a pacientes con diagnóstico de trastorno bipolar no estable.
TB: trastono bipolar.

6.8 PREVALENCIA DEL TRASTORNO BIPOLAR

Encontramos que la prevalencia del trastorno bipolar en esta muestra psiquiátrica era baja. Teniendo en cuenta el número total de pacientes evaluados, alrededor del 3,1% tenía un diagnóstico de trastorno bipolar (n=21.674/691.526) en algún momento del seguimiento. Si se tienen en cuenta únicamente los pacientes con un diagnóstico estable bipolar, éstos representan el 0,4% de la muestra (n=2.718/691.526); igual que la tasa de prevalencia hallada en nuestro estudio para el trastorno bipolar en la Comunidad de Madrid (estimando la población media de la Comunidad de Madrid entre los años 1.980 y 2009 con los datos del Instituto Nacional de Estadística), sólo el 0,4% tuvo un diagnóstico de trastorno bipolar (n=21.674/5.557.000) en el periodo de estudio.

6.9 FACTORES RELACIONADOS CON LA ESTABILIDAD DIAGNÓSTICA DEL TRASTORNO BIPOLAR

Se ha realizado una regresión logística para contrastar el efecto de las variables sociodemográficas sobre el estado de diagnóstico estable o no estable de trastorno bipolar. Se contrastaron las siguiguientes variables: género, estado civil, nivel educativo, situación laboral, ocupación, tipo de convivencia y antecedentes; ya descritos en Factores sociodemográficos.

El modelo obtenido presentaba un ajuste bueno (Chi^2 Hosmer y Lemeshow =8,054, gl=8, p= 0,428), clasificando correctamente al 80,5 % de la muestra para un valor de corte de 0,5 en la ecuación de regresión. Las cuatro variables que se incluyen en el modelo son estado civil (Chi^2 Wald=12,429, gl=4, p=0.014), nivel educativo (Chi^2 Wald=28,665, gl=8, p<0.001), situación laboral (Chi^2 Wald=15,737, gl=10, p=0,107) y antecedentes personales de asistencia psiquiatrica (Chi^2 Wald=115,714, gl=2, p<0,001). (Tabla 21).

Los odds ratios (OR) para estas variables (Tabla 21), muestran que con un estado civil de soltero aumenta el riesgo de tener un diagnóstico no estable de trastorno bipolar respecto a estar casado (OR=0,85; IC95%=0,74-0,98). El ser licenciado frente a analfabeto aumenta el riesgo de diagnóstico estable a casi el doble (OR=1,89; IC95%=1,22-2,92). El estar realizando el servicio militar respecto a ser ama de casa aumenta ligeramente el riesgo (OR=1,54; IC95%=0,46-5,13). Los pacientes que reciben un diagnóstico de trastorno bipolar en un ámbito hospitalario tienen el doble de riesgo de que este diagnóstico sea estable que aquellos que no tienen antecedentes previos (OR=2,03; IC95%=1,76-2,34).

	B	S.E.	Wald	df	Sig.	OR	95% C.I.for EXP(B) Lower	Upper
ESTADO CIVIL (referencia Casado)			12,429	4	,014			
Estado civil: Divorciado	,250	,162	2,378	1	,123	1,283	,935	1,763
Estado civil: Soltero	-,158	,071	4,901	1	,027	0,854	,742	,982
Estado civil: Viudo	,186	,112	2,756	1	,097	1,205	,967	1,501
Estado civil: Separado	-,027	,135	,040	1	,841	0,973	,747	1,268
NIVEL EDUCATIVO (referencia Analfabeto)			28,665	8	,000			
Nivel educativo: Sin estudios	,062	,183	,116	1	,733	1,064	,743	1,525
Nivel educativo: Primaria	,050	,174	,081	1	,775	1,051	,748	1,477
Nivel educativo: Graduado escolar	,070	,181	,151	1	,697	1,073	,753	1,529
Nivel educativo: Bachillerato	,227	,188	1,466	1	,226	1,255	,869	1,812
Nivel educativo: COU	,314	,202	2,413	1	,120	1,369	,921	2,033
Nivel educativo: Titulado	,465	,199	5,448	1	,020	1,592	1,077	2,352
Nivel educativo: Licenciado	,638	,223	8,185	1	,004	1,892	1,222	2,928
Nivel educativo: Otros	,060	,320	,035	1	,852	1,062	,567	1,988
SITUACIÓN LABORAL (referencia Labores de casa)			15,737	10	,107			
Situación laboral: Servicio militar	,436	,612	,508	1	,476	1,547	,466	5,134
Situación laboral: ILT	-,065	,115	,322	1	,570	0,937	,749	1,173
Situación laboral: ILP	-,149	,189	,623	1	,430	0,861	,594	1,248
Situación laboral: Activo	,039	,082	,225	1	,635	1,040	,885	1,222
Situación laboral: Buscando primer empleo	-,066	,306	,047	1	,828	0,936	,514	1,703
Situación laboral: Parado con subsidio	,097	,168	,332	1	,564	1,101	,793	1,530
Situación laboral: Parado sin subsidio	-,222	,132	2,835	1	,092	0,801	,619	1,037
Situación laboral: Jubilación	,162	,091	3,206	1	,073	1,176	,985	1,405
Situación laboral: Rentista	-,410	,498	,677	1	,411	0,664	,250	1,761
Situación laboral: Estudiando	-,293	,162	3,266	1	,071	0,746	,543	1,025
ANTECEDENTES DE ASISTENCIA (referencia Sin antecedentes)			115,714	2	,000			
Antecedentes: Diagnóstico ambulatorio	,100	,067	2,237	1	,135	1,106	,969	1,261
Antecedentes: Diagnóstico hospitalario	,710	,072	97,878	1	,000	2,034	1,767	2,341
Constante	-1,766	,178	98,719	1	,000	0,171		

Tabla 21. Regresión logística para variables sociodemográficas.
COU: Curso de Orientación Universitaria. **ILT:** Incapacidad Laboral Temporal. **ILP:** Incapacidad Laboral Permanente.

7 DISCUSIÓN

Resumen

Este estudio abordó el tema de la estabilidad diagnóstica en el trastorno bipolar en la Comunidad de Madrid. Los resultados mostraron una estabilidad muy pobre según los métodos de estudio y notablemente inferior a la encontrada en estudios anteriores. En el conjunto de la muestra, sólo el 18,3% de los pacientes mantuvieron los diagnósticos de trastorno bipolar en el 75% de las evaluaciones y se encontró que las consistencias tanto prospectiva como retrospectiva eran bajas. Algunas razones metodológicas podrían explicar las diferencias con estudios anteriores, especialmente el escaso número de evaluaciones y el período de seguimiento más corto utilizado por éstos, que puede no dar tiempo suficiente para llegar al diagnóstico correcto. Nuestro estudio tiene las limitaciones derivadas del diseño metodológico de cualquier estudio naturalista retrospectivo y también está limitado por la posible existencia de vías no controladas de atención psiquiátrica, pero puede reflejar con mayor precisión el proceso clínico "real", lo que pone en entredicho la precisión de los sistemas de evaluación clínica en condiciones de práctica clínica habitual. La prevalencia del trastorno bipolar en esta muestra psiquiátrica, del 0,4%, fue menor que la encontrada en otras poblaciones psiquiátricas, pero cercana a estudios más precisos. El estudio más detallado de los factores que influyen en la estabilidad del trastorno bipolar y un mejor conocimiento del curso de los diagnósticos a lo largo de su evolución se proponen como dos futuras líneas de investigación.

La evolución natural del trastorno bipolar es propensa a una alta variabilidad de su curso clínico, caracterizada por un patrón de episodios maníacos y depresivos con intervalos de períodos de eutimia. Sin embargo, los síntomas centrales de los episodios afectivos no están presentes con tanta frecuencia y la presencia de trastornos comórbidos frecuentes inducen a error en el diagnóstico durante la práctica clínica diaria (Blacker et Tsuang 1992; Ghaemi et al. 2000). En el presente estudio se encontró que la estabilidad del diagnóstico de trastorno bipolar era baja y menor que en estudios anteriores (Chen et al. 1998; Kessing 2005; Schwartz et al. 2000; Schimmelmann et al. 2005; Veen et al. 2004), con los tres índices diferentes utilizados. Los resultados de este trabajo son similares a los encontrados previamente en un estudio en diversos ámbitos de atención de la Comunidad de Madrid, aunque con una muestra y tiempo de seguimiento menores (Baca-Garcia et al. 2007).

El 27,4% de los pacientes recibieron un diagnóstico de trastorno bipolar en la primera evaluación y sólo el 18,3% de la muestra total fue considerado estable según los criterios establecidos en este estudio. Adicionalmente, se encontró una fluctuación diagnóstica de los diagnósticos habituales incluidos en el diagnóstico diferencial del trastorno bipolar. Todas estas conclusiones se detallan y comentan en las siguientes secciones.

7.1 DIAGNÓSTICO DE TRASTORNO BIPOLAR EN LA PRIMERA EVALUACIÓN

Los errores de diagnóstico en el trastorno bipolar son especialmente frecuentes en el primer contacto con el médico, los síntomas iniciales engañosos de una presentación enmascarada debido al abuso de sustancias, los síntomas depresivos o psicóticos pueden explicar en parte estas dificultades. Mientras que sólo el 27,4% de los sujetos recibió el diagnóstico de trastorno bipolar en la primera evaluación, el resto recibió el diagnóstico al menos una vez durante evaluaciones posteriores. Resultados similares fueron presentados en un estudio anteriormente (Kessing 2005), donde se señalaba que estas cifras eran consistentes con la alta prevalencia de diagnósticos erróneos del 48% y 69% encontrados en investigaciones naturalistas usando cuestionarios autoadministrados en consultas de médicos en general (Hirschfeld et al. 2003;7 Lish et al. 1994).

Sin embargo, en nuestra muestra el 50,5% de los pacientes que recibió el diagnóstico de trastorno bipolar en la primera evaluación se mantuvo con el diagnóstico estable en tres cuartas partes de las evaluaciones; esto no concuerda con la cifra reportada por Chen et al. en 1998, quienes señalaron que alrededor del 70% de los sujetos con un diagnóstico inicial de trastorno bipolar no cambiaron a uno diferente. Por otro lado, el porcentaje de los pacientes con un diagnóstico estable de trastorno bipolar (n=2.718) que fueron correctamente diagnosticados en la primera evaluación (n=2.016) aumenta en nuestra muestra hasta un 74,2%. Estos resultados apoyan la hipótesis de la dificultad diagnóstica del trastorno bipolar en las primeras evaluaciones.

7.2 DIAGNÓSTICO DE TRASTORNO BIPOLAR EN LA ÚLTIMA EVALUACIÓN

La última evaluación mostró un aumento en el número de diagnósticos de trastorno bipolar (37,1% de la muestra) y, de ésos, el 42,6% había sido estable a lo largo del estudio. Por otro lado, el 84,6% de los pacientes con diagnósticos estables (n=2.718) fueron diagnosticados con precisión en su última consulta (n=2.299).

Este resultado puede reflejar un aumento progresivo en la estabilidad del diagnóstico a lo largo de las evaluaciones (en nuestro caso en un número mínimo de diez), lo que es congruente con la idea de que el rediagnóstico rutinario podría mejorar las posibilidades de un proceso de diagnóstico exitoso. Sin embargo, Schwartz et al. en 2000 informaron que la consistencia retrospectiva del trastorno bipolar fue del 85% cuando se compararon los diagnósticos de 6 y 24 meses, pero se redujo al 73% cuando se compararon los diagnósticos iniciales y los de 24 meses. Esto significaría que las tasas de consistencia para algunos diagnósticos disminuyeron a medida que aumentaba el período de seguimiento. En cualquier caso, la consistencia retrospectiva del trastorno bipolar de nuestro estudio (37,5%) es baja en comparación con otros estudios que la midieron (58,4-94,4%), es similar a la presentada por Baca-García et al. en 2007 (38%) y mayor que la de Weeke et al. de 1984 (20%). Una entrevista estructurada, la Entrevista Clínica Estructurada para el DSMIII-R (SCID) proporcionó los diagnósticos psiquiátricos del DSM-III-R en el estudio de Schwartz et al. Tal vez, el uso de entrevistas semiestructuradas hubiera mejorado la fiabilidad y, por lo tanto, la estabilidad diagnóstica.

7.3 ESTABILIDAD DIAGNÓSTICA DEL TRASTORNO BIPOLAR

Hasta donde sabemos, éste ha sido el mayor estudio longitudinal, 14.557 pacientes a lo largo de 30 años de estudio, que ha evaluado la estabilidad diagnóstica del trastorno bipolar en condiciones ecológicas. Kessing en 2005 mencionó que ningún estudio había investigado la estabilidad diagnóstica de los diagnósticos psiquiátricos más comunes de la CIE-10 administrados en condiciones clínicas ecológicas. Este es el caso de nuestro estudio, que ha mostrado una baja estabilidad de las categorías de trastorno bipolar de la CIE-10, medida por su consistencia temporal y constancia diagnóstica; y considerablemente menor que en estudios anteriores. Las razones de estas diferencias en la estabilidad temporal diagnóstica no están claras, pero pueden deberse al gran tamaño de la muestra, la extensa duración del seguimiento, el alto número de evaluaciones, los criterios diagnósticos o las variables sociodemográficas.

La consistencia temporal mostró resultados bajos con una consistencia prospectiva del 50,8% y una consistencia retrospectiva del 37,5%. Cabe señalar que el valor de kappa fue bajo (kappa=0,17) entre el primer y el último diagnóstico. No obstante, dado que los valores kappa tienen en cuenta los casos positivos estables y los casos negativos estables, pero también los casos que remiten y los casos nuevos, pueden observarse valores kappa bajos si se produce un elevado número de casos nuevos o que remiten (Mattanah et al. 1995) y, por lo tanto, no reflejan necesariamente una falta de estabilidad diagnóstica.

Los resultados de nuestro estudio mostraron que sólo el 18,3% de los pacientes tenían el diagnóstico de trastorno bipolar en el 75% de las evaluaciones. En estos pacientes con diagnóstico estable, el número medio de evaluaciones hasta el primer diagnóstico de trastorno bipolar fue de 3,7 y un tiempo medio de 318,1 días. Estos valores se incrementaron a 21,2 evaluaciones y 1.511,2 días dentro del grupo con diagnostico no estable. Así, los pacientes con diagnóstico estable de trastorno bipolar se diagnosticaban antes (menos de un año) y necesitaban un menor número de evaluaciones que los que no tenían un diagnóstico estable (algo más de 4 años hasta que se realizaba el diagnóstico bipolar).

En nuestro estudio, los pacientes con diagnóstico bipolar estable consiguieron esa estabilidad diagnóstica a los 7.386,7 días (algo más de 20 años) y 279 visitas de seguimiento. Y a los pacientes con diagnóstico no estable se les retiró ese diagnóstico a los 2.929 días (8 años aproximadamente) y tras 55 evaluaciones. Estos resultados podrían estar en consonancia con los informes anteriores de Hirschfeld en 2003 y Baldesarini en 1999, que informaban de un retraso en el diagnóstico correcto, que en muchos casos podría ser de unos 8-10 años desde el inicio de la enfermedad (Hirschfeld et al 2003; Baldessarini et al. 1999). Por tanto, en nuestro estudio, los datos hacen inferir que, tanto consolidar como retirar el diagnóstico de trastorno bipolar, es una tarea que precisa de muchos años de seguimiento y un alto número de evaluaciones. En este sentido, consolidar el diagnóstico bipolar costaba unas 14 visitas/año, mientras que retirar este diagnóstico conllevaba menos de 7 visitas/año. Este hecho puede reflejar que, los pacientes con diagnóstico estable de trastorno bipolar, son más complejos o graves que aquellos a los que se acaba retirando este diagnóstico, y además precisan de mayor atención sanitaria.

Aunque no era un objetivo principal de nuestro estudio, se encontraron cuatro variables relacionadas con la estabilidad diagnóstica del trastorno bipolar: estado civil, nivel educativo, situación laboral y antecedentes personales de asistencia psiquiátrica. En otro estudio preliminar (Baca-García et al. 2007) encontraron cuatro variables relacionadas con la estabilidad del

diagnóstico bipolar: sexo, edad ≥ 40 años, número de consultas psiquiátricas y los Centros de Salud Mental ambulatorios. En cualquier caso, se necesitan más estudios centrados en estas variables para confirmar o rechazar estas conclusiones.

El hecho de que los facultativos tratantes a menudo tengan acceso a registros y diagnósticos anteriores, puede resultar en una inclinación a mantener el diagnóstico previo en lugar de asignar uno diferente. Sin embargo, este posible sesgo no está respaldado por los valores sorprendentemente bajos de estabilidad temporal diagnóstica de los diagnósticos de trastornos mentales crónicos que utilizan una metodología similar en una muestra adulta tratada por el mismo equipo de psiquiatras y psicólogos (Baca-Garcia et al. 2007).

Las mayores tasas de consistencia encontradas por otros autores (Chen et al. 1998; Kessing 2005; Schwartz et al. 2000; Schimmelmann et al. 2005; Veen et al. 2004) pueden haber sido influenciadas por una serie de inconvenientes que disminuyen la generalizabilidad de estos estudios: la mayoría de los estudios que han evaluado la estabilidad del trastorno bipolar tienen períodos de seguimiento más cortos que el presente estudio y hay un escaso número de evaluaciones en la mayoría de los estudios.

7.4 ERRORES DIAGNÓSTICOS EN EL TRASTORNO BIPOLAR

Los pacientes con un diagnóstico estable de trastorno bipolar presentaron alguna fluctuación diagnóstica que incluía los diagnósticos típicos incluidos en el diagnóstico diferencial del trastorno bipolar. Los trastornos que presentaron la mayor confusión diagnóstica con el trastorno bipolar fueron, en orden de importancia: otros trastornos afectivos, trastornos neuróticos y de ansiedad, trastornos del espectro de la esquizofrenia y trastornos de la personalidad. Estos resultados fueron similares tanto para los diagnósticos iniciales como para los realizados en la última evaluación.

En nuestro estudio se hallaron unas altas tasas de error diagnóstico del trastorno bipolar con otros trastornos afectivos: un 44,5% de los pacientes que fueron diagnosticados en la primera evaluación de un trastorno afectivo no bipolar acabaron siendo diagnosticados en la última visita de seguimiento con trastornos bipolares; y 51% de los pacientes que fueron diagnosticados de trastorno bipolar al inicio ya no lo estaban en la última evaluación. Estudios previos coinciden en explicar las altas tasas de diagnósticos erróneos derivados de la confusión con la depresión unipolar (Hirschfeld et al. 2003;7 Lish et al. 1994), sobre todo en los casos en que el trastono bipolar debuta con uno o varios episodios depresivos. En cuanto a los trastornos neuróticos y de ansiedad englobados en las categorías F40-F49, el porcentaje de estos diagnósticos al inicio del seguimiento es elevado (21,03%) de los pacientes que acaban siendo diagnosticados de trastorno bipolar en última instancia. Otros errores diagnósticos menos frecuentes se dieron con el espectro de la esquizofrenia (7,5% al inicio y 8,3% al final) y con los trastornos de personalidad (4,2% iniciales y 3,6% finales).

7.5 PREVALENCIA DEL TRASTORNO BIPOLAR

La estabilidad diagnóstica juega un papel importante en la estimación precisa tanto de la prevalencia como de la incidencia. Mientras que la incidencia es una medida del riesgo, la prevalencia está influenciada por la duración del episodio (pronóstico) y por la mortalidad (Burger et Neeleman 2007). Idealmente, debería ser posible clasificar las asociaciones que se observan en los datos de prevalencia epidemiológica según sus principales determinantes: incidencia y duración del episodio (Patten 2005); una medida intermedia a alcanzar es la descripción precisa de la estabilidad diagnóstica de la enfermedad.

Encontramos que la prevalencia del trastorno bipolar en esta muestra psiquiátrica era baja. Teniendo en cuenta el número total de pacientes evaluados, alrededor del 3,1% tenía un diagnóstico de trastorno bipolar (n=21.674/691.526) en algún momento del seguimiento. Si se tienen en cuenta únicamente los pacientes con un diagnóstico estable bipolar, éstos representan el 0,4% de la muestra (n=2.718/691.526); igual que la tasa de prevalencia hallada en nuestro estudio para el trastorno bipolar en la Comunidad de Madrid (estimando la población media de la Comunidad de Madrid entre los años 1.980 y 2009), sólo el 0,4% tuvo un diagnóstico de trastorno bipolar (n=21.674/5.557.000) en el periodo de estudio. Estas cifras son menores que las encontradas en la mayoría de los otros estudios realizados en la población general y psiquiátrica (Bijl et al. 1998; ten Haven et al. 2002; Waraich et al. 2004; Angst 1995; Kessler et al. 1994; Haro et al. 2006; Bland et al. 1988) aunque no todas (Perala et al. 2007; Pini et al. 2005); y son similares a las obtenidas previamente por Baca-García et al. en 2007 con una muestra y tiempo de seguimiento menores. Nuestros resultados sobre la prevalencia son comparables a los de Perala et al. (2007), quienes informaron que el National Hospital Discharge Register era el medio más fiable de detección del trastorno psicótico y bipolar y encontraron una prevalencia de por vida del 0,2% para el trastorno

bipolar. En este trabajo, la diferencia con las encuestas de población se explicó sobre la base de los posibles falsos positivos en las entrevistas estructuradas, como la Entrevista Diagnóstica Internacional Compuesta (CIDI), en comparación con el uso de múltiples fuentes de información (Perala et al. 2007). Los estudios como el nuestro, en los que se hace un seguimiento de los pacientes durante largos períodos, están más cerca de este enfoque que los ensayos clínicos basados en calendarios de diagnóstico y entrevistas realizadas en una unidad de investigación durante un período corto o en grandes estudios epidemiológicos transversales basados en una única evaluación.

El uso de un número mínimo de diez evaluaciones como criterio para ser incluido en la muestra puede haber disminuido el número de pacientes bipolares, aunque parece muy improbable que un paciente que padece realmente un trastorno bipolar no hubiera consultado al menos diez veces en el período de estudio. Incluso teniendo en cuenta a las personas diagnosticadas y tratadas en consultas privadas que no se incluirían en la muestra, estas cifras son considerablemente bajas dado que los servicios psiquiátricos españoles son de fácil acceso para las personas de la comunidad.

7.6 FORTALEZAS Y LIMITACIONES

Las principales fortalezas de este estudio son el gran tamaño muestral que supone la población atendida en los Centros de Salud Mental de la Comunidad de Madrid y que la representa en su casi totalidad, la duración del seguimiento (durante 30 años, con una media de seguimiento de 9 años) y el elevado número de evaluaciones (mediana=38). Cabe destacar también que la evaluación de la estabilidad del trastorno bipolar se realizó en un ámbito clínico ambulatorio, de forma que el procedimiento de diagnóstico se ajustaba a la práctica clínica habitual. Los facultativos que asignaron los diagnósticos estaban ciegos para estudiar los procedimientos. Otros estudios publicados han utilizado entrevistas semiestructuradas y otros instrumentos de diagnóstico no utilizados habitualmente en la práctica clínica para mejorar la fiabilidad. Los resultados de nuestro estudio se basaron en el uso de diagnósticos CIE-10 establecidos clínicamente y aunque la fiabilidad puede haber sido afectada, posiblemente reflejan con mayor precisión el uso real de las clasificaciones diagnósticas en la práctica psiquiátrica y pueden ser más útiles para estimar la utilidad clínica de los sistemas actuales de clasificación psiquiátrica. El profesional establece un diagnóstico basado en los criterios del sistema CIE-10, pero la validez de estos criterios se comprueba en la práctica diaria mediante la información fenomenológica recogida sobre el paciente además de los criterios diagnósticos (Sandanger et al. 2002).

Las limitaciones de nuestro estudio son comunes a la mayoría de las encuestas a gran escala e inherentes a un estudio naturalista retrospectivo, que se realizó en condiciones del mundo real (Das et Grover 2007). Las entrevistas clínicas estructuradas o semiestructuradas no se utilizaron en este estudio para el diagnóstico de trastorno bipolar con criterios CIE-10. Los facultativos que asignaron los diagnósticos no fueron entrenados específicamente para aumentar la fiabilidad entre los evaluadores, pero todos ellos trabajaban en un sistema de salud público. Es probable que una mayor fiabilidad entre los evaluadores hubiera aumentado la estabilidad del diagnóstico al reducir los errores aleatorios.

En el estudio que se presenta hubo un sesgo de selección de casos, puesto que se han desestimados aquellos pacientes que, habiendo sido diagnosticados de trastorno bipolar en al menos una ocasión, tenían un seguimiento inferior a un año o habían recibido menos de 10 evaluaciones. Esto supuso que un tercio de la muestra inicial no fuese analizada. Eliminar estos pacientes, con escaso seguimiento y pocas valoraciones, podría suponer una infravaloración de la estabilidad diagnóstica.

Las vías alternativas de búsqueda de tratamiento son otro posible inconveniente de nuestro estudio clínico. La mayoría de los españoles reciben atención médica y de salud mental en los servicios públicos (MSyC 2007), pero no se puede descartar la existencia de un número de pacientes evaluados en consultas privadas tanto psiquiátricas como psicológicas. En el caso particular del trastorno bipolar es muy probable que hayan consultado en el servicio público psiquiátrico durante el largo periodo de estudio, especialmente por la sintomatología presente en episodios maníacos, pero es posible que no alcancen el número mínimo de consultas necesario para ser incluidos en nuestra muestra. Del mismo modo, los pacientes podrían haberse desplazado o haber buscado tratamiento en otro lugar durante el período de seguimiento, en particular aquellos con los diagnósticos más inestables, lo que provocaría un sesgo en la estabilidad diagnóstica. Sin embargo, hay algunas razones en contra de esta posibilidad. En primer lugar, aunque no se incluyen los cambios de residencia fuera de la Comunidad de Madrid, las tasas de cambio de residencia a otras provincias de España u otros países entre los jóvenes se estiman anualmente en menos del 2% (INE 2007).
Por otro lado, la selección intencional de sujetos con 10 o más visitas clínicas psiquiátricas, implica

que los resultados de esta investigación pueden no ser generalizados a aquellos sujetos con trastornos más transitorios y más leves.

El estudio de los factores implicados en la evolución del trastorno bipolar fue un objetivo secundario del presente estudio y finalmente se consideró que estaba fuera de su alcance. Nuestros resultados muestran que hay una influencia significativa de algunos de estos factores, sin embargo la recolección transversal de datos realizada únicamente en la evaluación inicial de los pacientes y no continuada a lo largo del estudio disminuye la fiabilidad de los resultados. Nuestra intención es generar nuevos estudios sobre esta materia, que combinen las evaluaciones longitudinales y la recolección longitudinal de los factores relevantes, para explorar su relación con la evolución del trastorno bipolar.

7.7 RELEVANCIA DEL ESTUDIO E INVESTIGACIONES FUTURAS

Muchos factores pueden estar involucrados en la evolución inestable de un diagnóstico psiquiátrico. Schwartz mencionó que los cambios diagnósticos a lo largo del tiempo podrían reflejar la evolución de una enfermedad, la aparición de nueva información o la falta de fiabilidad de las mediciones (Schwartz et al. 2000). La relativa falta de estabilidad en los diagnósticos a lo largo del tiempo en el presente estudio puede deberse a la evolución de la enfermedad o reflejar las debilidades inherentes a las evaluaciones clínicas.

No obstante, los hallazgos de la presente investigación plantean cuestiones preocupantes en cuanto a la validez de los resultados de la investigación epidemiológica, clínica y farmacológica psiquiátrica, en particular, en estudios de trastornos crónicos con períodos de seguimiento cortos que pueden no dar tiempo suficiente para llegar al diagnóstico correcto o en estudios que no tienen en cuenta el contexto. Los métodos reales de evaluación clínica pueden requerir revisiones adicionales para garantizar su fiabilidad.

El estudio de la estabilidad diagnóstica a partir de los métodos utilizados en nuestro estudio conforma el primer paso de un trabajo más amplio y esboza las posibilidades futuras. Sobre todo empleando las nuevas tecnologías informáticas con programas de recogida integrales de datos por parte del paciente, de los familiares, de los profesionales que le atienden en los diferentes ámbitos sanitarios... Nuestro grupo de trabajo ha publicado diversos artículos de los datos recogidos con el programa MEmind (Berrouiguet et al. 2016, 2017 y 2019; Barrigón et al. 2017 y 2017[2]; Lemey et al. 2019), que es una herramienta informática de recogida sistemática de datos.

Esperamos que el presente estudio contribuya también a enfatizar las importantes repercusiones de la inestabilidad diagnóstica, tal como se refleja en las diferencias existentes entre la prevalencia de comorbilidad en pacientes "estables" y "no estables".

A partir de aquí se puede iniciar la búsqueda de una mejor comprensión del curso temporal del trastorno bipolar y, por extensión, ser aplicable para consolidar otros diagnósticos psiquiátricos. La vía que sigue al diagnóstico psiquiátrico a lo largo de la evolución de la enfermedad suele atravesar diferentes categorías (Blacker et Tsuang 1992); su descripción precisa, que incluye las vías diagnósticas más frecuentes y los factores relacionados con el cambio diagnóstico, puede ayudar a programar las decisiones clínicas. El sistema de salud también podría beneficiarse de un sistema de diagnóstico que incluyera el funcionamiento y el pronóstico de la enfermedad, no sólo los diagnósticos descriptivos y ajustados a criterios clasificatorios (Sandanger et al. 2002).

8 CONCLUSIONES

1. En este trabajo se reflejó la práctica clínica real en la Comunidad de Madrid, con una recogida de datos durante 30 años, y mostró una baja estabilidad diagnóstica para los pacientes que en alguna ocasión fueron dignosticados de trastorno bipolar.
2. La constancia diagnóstica del trastorno bipolar en esta muestra fue baja. Sólo el 18,3% de los pacientes recibió este diagnóstico de forma consistente a lo largo del seguimiento.
3. Además, la mitad de los pacientes diagnosticados de trastorno bipolar en una primera consulta no mantenían el diagnóstico de forma estable.
4. Tanto la consistencia prospectiva como la retrospectiva del diagnóstico de trastorno bipolar eran menores que las reportadas en la literatura, pero similares con las halladas en un estudio previo realizado en la Comunidad de Madrid.
5. Se hallaron frecuentes errores diagnósticos en relación al trastorno bipolar. El más común era con otros trastornos afectivos.
6. Aunque se diagnosticó en menos de un año a los pacientes con trastorno bipolar estable, eran precisos 20 años de media para que este diagnóstco se consolidase.
7. También fue difícil retirar este diagnósto; fueron necesarios 8 años de media para dejar de diagnosticar a un paciente de trastorno bipolar.
8. Los pacientes con un trastorno bipolar estable consumieron más recursos sanitarios, precisaron el doble de consultas anuales que los pacientes a los que se retiró este diagnóstico.
9. La prevalencia del trastorno bipolar en esta muestra, representativa de la Comunidad de Madrid, fue del 0,4%; más baja que la prevalencia mundial del 1%.
10. Con los resultados de este estudio y la baja estabilidad diagnóstica encontrada, se cuestiona la validez de los actuales sistemas de clasificación diagnóstica, en este caso la CIE-10, para su aplicación en la práctica clínica diaria. El empleo de los criterios diagnósticos del trastorno bipolar en condiciones reales conlleva a errores diagnósticos.
11. Ante la dificultad diagnóstica del trastorno bipolar mostrada en este estudio, se hace preciso que, en la práctica clínica diaria, se adopten instrumentos diagnósticos que mejoren la fiabilidad diagnóstica, sobre todo en las primeras evaluaciones.
12. Aunque se hallaron algunos factores relacionados con la estabilidad diagnóstica del trastorno bipolar, son necesarios nuevos trabajos que estudien estas variables para facilitar la identificación de estos pacientes y realizar un diagnóstico acertado al inicio de la enfermedad.
13. Se sugiere que para futuros estudios sobre el trastorno bipolar se tenga en cuenta que el diagnóstico sea estable, y no se incluyan a pacientes con un diagnóstico realizado transversalmente que pueda falsear los resultados.
14. En las investigaciones futuras sobre el trastorno bipolar se deben incluir estudios prospectivos de seguimiento y ensayos clínicos para que este campo pueda avanzar. Los clínicos necesitan herramientas diagnósticas fiables para reducir los errores diagnósticos en el trastorno bipolar.

9 TABLAS

10 FIGURAS

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12 ANEXO I: Recogida de datos

Servicios de Salud Mental — Madrid

FECHA:____/____/____ **Nº HISTORIA:**

Nº SEGURIDAD SOCIAL: ___ / _____

APELLIDOS: 1º: _____ **2º:**_____

NOMBRE: _____ **Nº D.N.I.:** _____

DOMICILIO: _____ **C. POSTAL:** _____

TELÉFONO: _____/_____

FECHA DE NACIMIENTO: _____/_____/_____ **HOMBRE:** _____ **MUJER:** _____

ESTADO CIVIL:

SOLTERO/A:	_____S
CASADO/A:	_____C
DIVORCIADO/A:	_____D
SEPARADO/A:	_____X
VIUDO/A:	_____V

TIPO DE CONVIVENCIA:

SOLO/A:	_____01
CON CÓNYUGE:	_____02
CON PAREJA:	_____03
CON PADRES:	_____04
SOLO CON PADRE:	_____05
SOLO CON MADRE:	_____06
CON HIJOS:	_____07
CON OTROS FAMIL:	_____08
EN INSTITUCIÓN:	_____09
OTROS:	_____00

TIPO DE ESTUDIOS:

ANALFABETO/A:	_____01
SIN ESTUDIOS:	_____02
ESTUDIOS PRIMARIOS:	_____03
GRADUADO ESCOLAR:	_____04
BACHILLER:	_____05
COU:	_____06
TITUL. UNIVERSITARIO:	_____07
LICEN. UNIVERSITARIO:	_____08
OTROS:	_____09

OCUPACIÓN O PROFESIÓN:

SIN TRABAJO	_____00
PROFESIONALES Y TÉCNICOS:	_____01
DIRECTIVOS:	_____02
PERSONAL ADMINISTRATIVO:	_____03
VENDEDORES Y COMERCIANTES:	_____04
HOSTELERÍA Y SERV. DE SEGURIDAD:	_____05
AGRICULTURA Y GANADERÍA:	_____06
PERSONAL DE INDUSTRIA, CONSTRUCCIÓN Y TRANSPORTE:	_____07
OTROS:	_____08
PERSONAL FUERZAS ARMADAS:	_____09

SITUACIÓN LABORAL:

TRABAJANDO :	_____02
BUSCANDO PRIMER EMPLEO:	_____03
PARADO CON SUBSIDIO:	_____04
PARADO SIN SUBSIDIO:	_____05
RETIRADO, PENSIONISTA, JUBILADO:	_____ 06
ESTUDIANDO:	_____08
DEDICADO LABORES DEL HOGAR:	_____09
INCAPACIDAD LABORAL TRANS.:	_____10
INCAPACIDAD PERMANENTE:	_____11

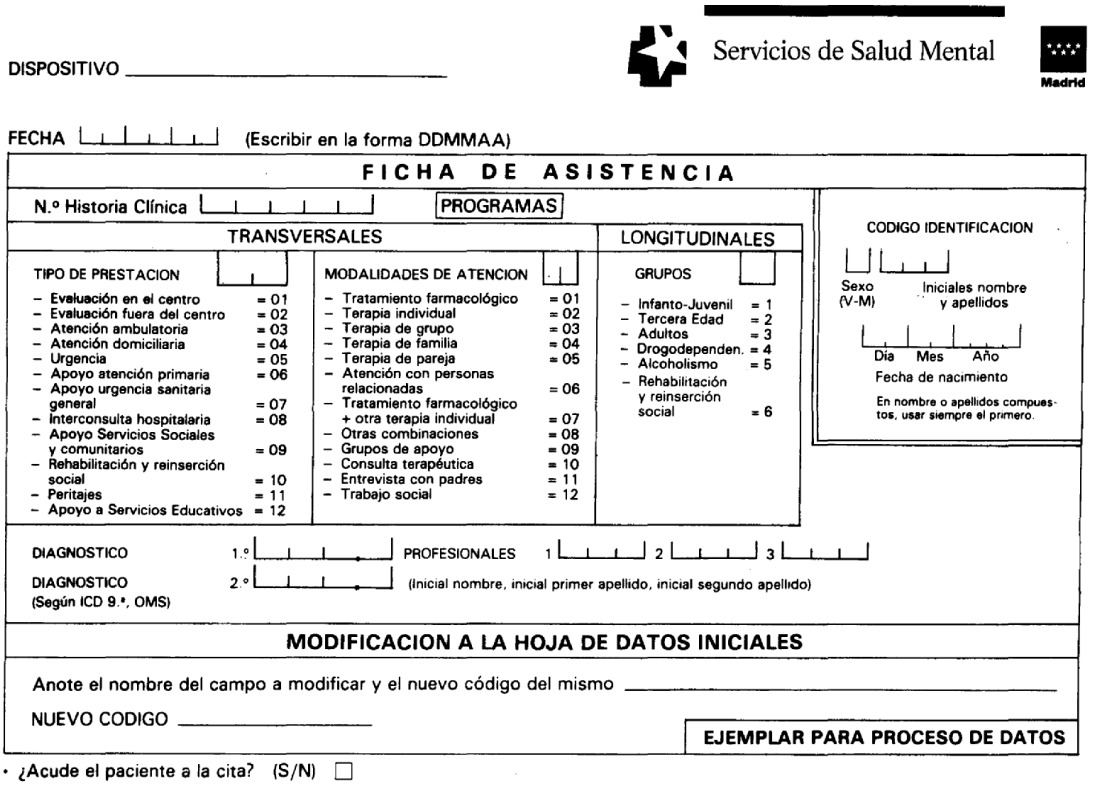
NOMBRE DEL CONSULTORIO: _____

NOMBRE DEL MÉDICO DE CABECERA: _____

¿HA TENIDO CONTACTO CON PSIQUIÁTRA O PSICÓLOGO ANTERIORMENTE?:

SI: _____ **¿DE QUÉ TIPO?:** PARTICULAR: _____ A; AMBULATORIO: _____ A; HOSPITALARIO: _____ H NO: _____

Ficha para la recogida de datos socio-laborales de los pacientes.



DISPOSITIVO _____

Servicios de Salud Mental

Madrid

FECHA ⌊⌊⌊⌊⌊⌊ (Escribir en la forma DDMMAA)

FICHA DE ASISTENCIA

N.º Historia Clínica ⌊⌊⌊⌊⌊⌊ PROGRAMAS

TRANSVERSALES

TIPO DE PRESTACION ⌊⌊

- Evaluación en el centro = 01
- Evaluación fuera del centro = 02
- Atención ambulatoria = 03
- Atención domiciliaria = 04
- Urgencia = 05
- Apoyo atención primaria = 06
- Apoyo urgencia sanitaria general = 07
- Interconsulta hospitalaria = 08
- Apoyo Servicios Sociales y comunitarios = 09
- Rehabilitación y reinserción social = 10
- Peritajes = 11
- Apoyo a Servicios Educativos = 12

MODALIDADES DE ATENCION ⌊⌊

- Tratamiento farmacológico = 01
- Terapia individual = 02
- Terapia de grupo = 03
- Terapia de familia = 04
- Terapia de pareja = 05
- Atención con personas relacionadas = 06
- Tratamiento farmacológico + otra terapia individual = 07
- Otras combinaciones = 08
- Grupos de apoyo = 09
- Consulta terapéutica = 10
- Entrevista con padres = 11
- Trabajo social = 12

LONGITUDINALES

GRUPOS ⌊⌊

- Infanto-Juvenil = 1
- Tercera Edad = 2
- Adultos = 3
- Drogodependen. = 4
- Alcoholismo = 5
- Rehabilitación y reinserción social = 6

CODIGO IDENTIFICACION

⌊⌊ ⌊⌊⌊

Sexo (V-M) Iniciales nombre y apellidos

⌊⌊⌊⌊⌊⌊

Día Mes Año

Fecha de nacimiento

En nombre o apellidos compuestos, usar siempre el primero.

DIAGNOSTICO 1.º ⌊⌊⌊.⌊

DIAGNOSTICO 2.º ⌊⌊⌊.⌊

(Según ICD 9.ª, OMS)

PROFESIONALES 1 ⌊⌊⌊ 2 ⌊⌊⌊ 3 ⌊⌊⌊

(Inicial nombre, inicial primer apellido, inicial segundo apellido)

MODIFICACION A LA HOJA DE DATOS INICIALES

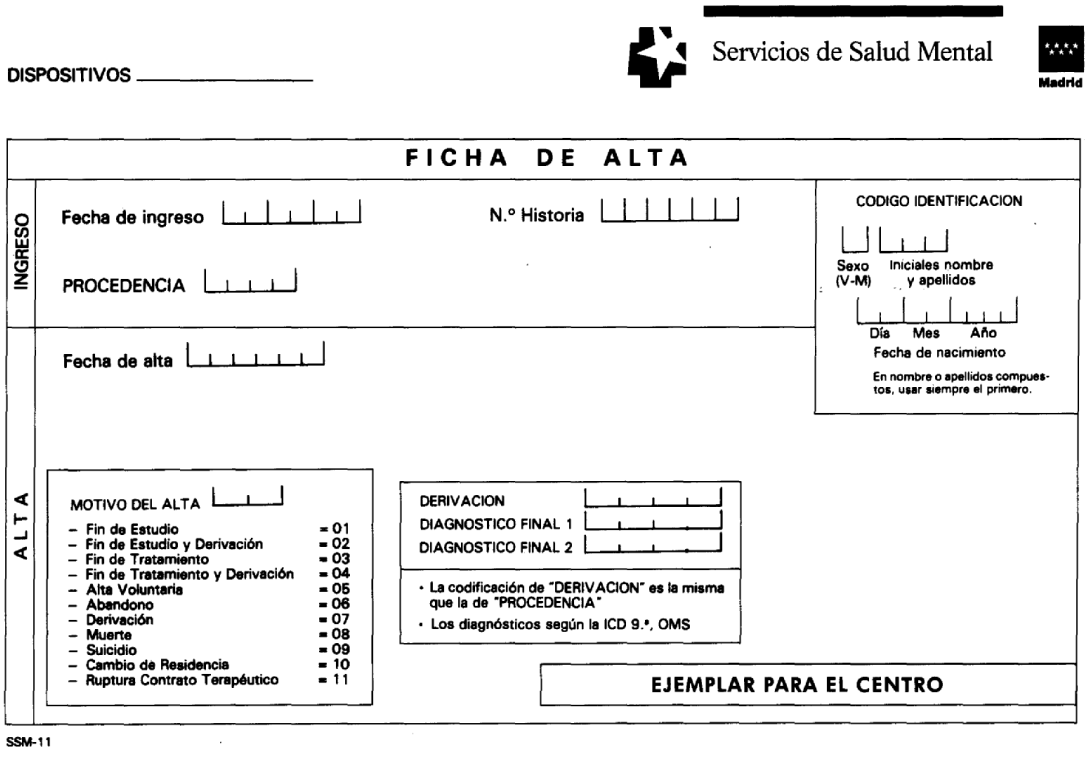
Anote el nombre del campo a modificar y el nuevo código del mismo _____

NUEVO CODIGO _____

EJEMPLAR PARA PROCESO DE DATOS

• ¿Acude el paciente a la cita? (S/N) ☐

Ficha de asistencia en consulta, donde se especifica el tipo de prestación, la modalidad de atención y el diagnóstico.



DISPOSITIVOS _____

Servicios de Salud Mental

Madrid

FICHA DE ALTA

INGRESO

Fecha de ingreso ⌊⌊⌊⌊⌊⌊ N.º Historia ⌊⌊⌊⌊⌊⌊

PROCEDENCIA ⌊⌊⌊⌊

ALTA

Fecha de alta ⌊⌊⌊⌊⌊⌊

CODIGO IDENTIFICACION

⌊⌊ ⌊⌊⌊

Sexo (V-M) Iniciales nombre y apellidos

⌊⌊⌊⌊⌊⌊

Día Mes Año

Fecha de nacimiento

En nombre o apellidos compuestos, usar siempre el primero.

MOTIVO DEL ALTA ⌊⌊

- Fin de Estudio = 01
- Fin de Estudio y Derivación = 02
- Fin de Tratamiento = 03
- Fin de Tratamiento y Derivación = 04
- Alta Voluntaria = 05
- Abandono = 06
- Derivación = 07
- Muerte = 08
- Suicidio = 09
- Cambio de Residencia = 10
- Ruptura Contrato Terapéutico = 11

DERIVACION ⌊⌊⌊⌊

DIAGNOSTICO FINAL 1 ⌊⌊⌊.⌊

DIAGNOSTICO FINAL 2 ⌊⌊⌊.⌊

- La codificación de "DERIVACION" es la misma que la de "PROCEDENCIA"
- Los diagnósticos según la ICD 9.ª, OMS

EJEMPLAR PARA EL CENTRO

SSM-11

Ficha para el alta de un paciente, se especifica el motivo y el/los diagnóstico/s final/es.

13 ARTÍCULOS

Rev Psiquiatr Salud Ment (Barc.). 2012;5(2):89–97

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental

ORIGINAL ARTICLE

Early detection of hypomania episodes in patients with affective disorder☆

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KEYWORDS
Bipolar disorder;
HCL-32;
Hypomania;
Major depression;
Prevalence

Abstract
Introduction: Bipolar disorder (BP) is one of the major causes of disability in the world. Epidemiological studies suggest that this disorder could be under-diagnosed owing to the difficulty in detecting hypomania episodes. The detection of present and past episodes of hypomania could help in the diagnosis and appropriate treatment of this disorder. The Hypomania Check List (HCL-32) is a questionnaire validated into Spanish and designed to detect past and present hypomania episodes in the psychiatric patient population.
Materials and methods: A total of 128 patients over 18 years old and diagnosed with type I bipolar (BP-I) disorder (n = 1), type II bipolar (BP-II) disorder (n = 30), major depression (MD) (n = 57), anxiety disorders (AD) (n = 15) were selected, along with a control group (C) (n = 25). The patients were diagnosed according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IVTR). Screening for hypomania episodes was carried out by applying the HCL-32 scale.
Results: The area under the ROC curve was 0.65 with a 95% confidence interval (CI) of 0.55–0.75. The chosen cut-off point of the HCL-32 was 15. The values for the sensitivity (Se), specificity (Sp), positive predictive values (PPV) and negative predictive values (NPV), and the prevalence (*P*) of hypomania episodes in the patients of the UP depression, for a cut-off point of 15 were: Se = 71.4%, 95% CI; 57.8, 85.1, Sp = 45.8%, 95% CI; 34.5–57.1, PPV = 43.75%, 95% CI; 32.25–55.25, NPV: 73.08%, 95% CI; 60.06–86.09 and *P* = 67.2%.
Conclusions: The HCL-32 is a very sensitive, but not very specific, screening tool. This could partly explain the high proportion of hypomania episodes detected in our sample. Unlike previous studies, our sample is heterogeneous (from different environments) and at a more severe and unstable clinical level. Future research should develop more specific measuring tools, and with greater external validation, for hypomania episodes.

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2173-5050/$ – see front matter

PALABRAS CLAVE
Trastorno bipolar;
HCL-32;
Hipomanía;
Depresión mayor;
Prevalencia

Detección precoz de episodios de hipomanía en pacientes con trastorno afectivo

Resumen
Introducción: El trastorno bipolar (TBP) es una de las causas más importantes de discapacidad en el mundo. Estudios epidemiológicos sugieren que este trastorno podría estar infradiagnosticado debido a la dificultad de detección de episodios de hipomanía. La detección de episodios de hipomanía, tanto actuales como pasados, permitiría el diagnóstico y tratamiento adecuados de este trastorno. La Lista de Valoración de Hipomanía (HCL-32) es un cuestionario validado al español diseñado para la detección de episodios de hipomanía, pasados y presentes. Con este estudio se pretende comprobar la utilidad de la HCL-32 para detectar los episodios de hipomanía en la población psiquiátrica.
Material y métodos: Se seleccionan 128 sujetos mayores de 18 años diagnosticados de trastorno bipolar tipo I (TBP-I) (n = 30), trastorno bipolar tipo II (TBP-II) (n = 1), depresión unipolar (DM) (n = 57), trastornos de ansiedad (TA) (n = 15) y un grupo control (C) (n = 25) de acuerdo con los criterios diagnósticos del Manual Diagnóstico y Estadístico de los Trastornos Mentales, cuarta edición, texto revisado, (DSM-IVTR). El cribado de episodios de hipomanía se realiza mediante la aplicación de la escala HCL-32.
Resultados: El área bajo la curva ROC = 0,65 IC95% (0,55-0,75). El punto de corte de la HCL-32 elegido es el 15. Los valores de sensibilidad (S), especificidad (E), valores predictivos positivo (VPP) y negativo (VPN) y prevalencia de episodios de hipomanía en los pacientes del grupo de depresión (P) para el punto de corte 15 son: S = 71,4%, IC95% (57,8, 85,1), E = 45,8%, IC95% (34,5-57,1), VPP = 43,75%, IC95% (32,25-55,25), VPN: 73,08%, IC95% (60,06-86,09) y P = 67,2%.
Conclusiones: La HCL-32 constituye un instrumento de cribado muy sensible, aunque poco específico. Esto explicaría, en parte, la elevada proporción de episodios de hipomanía que detectamos en nuestra muestra. A diferencia de estudios previos, nuestra muestra es heterogénea (procede de diferentes ámbitos) y a nivel clínico es más grave e inestable. Futuras investigaciones deberían desarrollar instrumentos de medición de episodios de hipomanía más específicos y con mayor validez externa.

Introduction

Bipolar disorder (BP) is a source of morbidity and mortality, with serious detriment to quality of life for those who suffer from it. In addition, due to its severity and chronicity, it involves a great social and economic expense.[1–3]

In the past, population studies demonstrated that, according to DSM-IV-TR criteria, BP has a prevalence of approximately 0.5–1.5%.[4,5]

Epidemiological studies from the western world suggest that BP may be under-diagnosed. This is attributed to the overdiagnosis of unipolar depression and the underdiagnosis of hypomanic episodes.[6] The most recent evidence suggests that the true prevalence rate lies between 5 and 5.5% of the population,[7–17] due in part to the underdiagnosed manic and hypomanic episodes.

It is estimated that the prevalence of major depression (MD) finally diagnosed as type I bipolar disorder (BP-I) rarely exceeds 5–10%.[18]

The rates oscillate between 30 and 61% for patients initially diagnosed with MD that are finally diagnosed with type II bipolar disorder (BP-II).[7,19–25]

The presence of hypomanic episodes is essential for the diagnosis of BP-II, establishing a differential diagnosis with MD. BP-I may also present hypomanic episodes, but the episodes differ from those of BP-II.

Over the course of the illness, patients diagnosed with BP-II seem more similar to those with bipolar disorder than those with a unipolar disorder, with respect to family history and response to treatment. In addition, BP-II responds better to treatment with mood stabilisers. Using antidepressants in these patients involves a higher risk of triggering an induced manic episode or rapid cycling.[26] Incorrect diagnosis could delay the start of adequate treatment, consequently worsening the prognosis.[17] Hence, the importance of an early diagnosis.

In an effort to improve the recognition of BP, instruments such as the Mood Disorder Questionnaire (MDQ)[27] and the Hypomania Checklist (HCL-32)[28] have been developed.

The HCL-32 is a self-administered questionnaire, serving as a tool designed to detect hypomanic components in patients with major depressive disorder.[28] This scale has recently been validated in Spanish. In the study performed for its validation, its usefulness over the MDQ scale for retrospectively diagnosing hypomanic episodes was highlighted.[14]

The objective of this study was to evaluate the validity of the HCL-32 scale in detecting hypomanic symptoms in a psychiatric population divided into 4 groups (MD, BP, AD and control), establish the best cut-off point for the scale and compare these results with those obtained in previously published studies.

Materials and methods

Patients and controls were recruited consecutively for the study between 2006 and 2010 in various areas:

2 mental health centres from Area 6 of the Madrid Community (Majadahonda and Villalba), and the emergency, short-stay and bipolar disorder units at the Puerta de Hierro University Hospital Psychiatry Department in Majadahonda.

The ethics committee from the Puerta de Hierro University Hospital in Majadahonda approved the study. Informed consent was obtained in writing from all patients before their inclusion in the study.

Subjects

The subjects who participated in this study were 18 years old or older, and diagnosed with BP-I, BP-II or MD, in accordance with DSM-IV-TR criteria. An anxiety disorder (AD) group was added, as some authors have affirmed that between 20 and 30% of patients who present anxiety symptomatology could have BP.[33] This way, we were able to assess whether there were significant differences from the rest of the groups. The AD group included patients who fulfilled DSM-IV criteria for generalised anxiety disorder. Patients were assigned to each group using the Mini-International Neuropsychiatric Interview (MINI).

The control group was selected among patients who came for consultation at the psychiatry department in mental health centres in Majadahonda and Villalba and at the emergency unit in the psychiatry department at the Puerta de Hierro University Hospital. Patients were included in this group if they were diagnosed with adjustment disorder and abnormal personality traits that did not compromise their overall functioning. Patients were excluded from this group if they fulfilled DSM-IV criteria for mood disorders, psychotic disorders or generalised anxiety disorder. We also excluded those with a score higher than 7 on the Hamilton Rating Scale for Depression (HRSD-17).

Initially, 131 patients were included; all of them provided their informed consent in writing. Of the total sample, 3 patients were excluded, as they did not fulfil inclusion criteria for any of the groups.

In a sample size of 133 subjects with unipolar depression, the expected prevalence of patients with hypomanic symptoms is 2/3 (66.7%), with an error of $\pm$8% and a 95% confidence interval (58.3–75.2%).

Among the 128 patients selected, 31 were diagnosed with BP (only 1 of them with BP-II), 57 with MD, 15 with AD and 25 were control subjects.

Patients were excluded from the study if they had previously been diagnosed with cognitive impairment or mental retardation. They were also excluded if they had a main diagnosis of alcohol or substance use disorder.

Procedure

After informing the patients about the study and obtaining their written informed consent for the study, the interviewer collected sociodemographic and clinical data. The interviewer applied the MINI, the HRSD-17, the Young Mania Rating Scale (YMRS) and the Clinical Global Impression Scale modified for bipolar disorder (CGI-BP) with each patient. The interviewer also gave each patient the HCL-32 questionnaire. The patients completed the International Personality Disorder Exam (IPDE) from the DSM-IV to study the relationship between personality disorders and hypomanic symptoms.

Hypomania screening among patients diagnosed with unipolar depression was performed by applying the HCL-32 scale. In this study we also aimed to corroborate the validation of the scale in Spanish, created by Vieta et al.[14] in 2007. To this end, the HCL-32 scale was applied to the control group and the group of patients diagnosed with BP.

Measurements

The HCL-32 scale is a self-administered questionnaire developed by Angst et al.[28] in 2005 and validated later in different countries and languages (German, English, Swedish, Italian, Chinese, Polish and Spanish). This scale consists of a list of possible hypomanic symptoms (32 items) to which the patient responds yes or no. In addition, it has 8 other sections that assess severity and impact of the symptoms on different aspects of the patient's life: (1) present state compared to normal state; (2) normal state compared to other people; (3) frequency of hypomanic periods; (4) socio-family and work consequences of said states; (5) others' reactions to these states; (6) general duration of these states; (7) existence of elevated mood in the last year; and (8) number of days with elevated mood in the last year. Total score for the HCL-32 is obtained by adding up the affirmative responses to the 32-hypomanic symptom list. The scale was accepted and validated in Spanish by Vieta et al.[14] who proposed 14 as the cut-off point for detecting hypomanic symptoms and discriminating between bipolar disorder and other groups (MD and healthy subjects). This cut-off point had a sensitivity of 0.85 with a 95% CI (0.78–0.91) and a specificity of 0.79 with a 95% CI (0.72–0.87).

Statistical analysis

The initial variables are described in tables with percentages and means, according to the variable type. Quantitative variables were summarised by mean and standard deviation (SD). In all cases, distribution of the variable was found according to theoretic models. An analysis of normality was performed using the Kolmogorov test. Confidence intervals were calculated at 95% (CI 95%) for the diagnostic tests, sensitivity, specificity and predictive values. The cut-off points for the HCL-32 scale were calculated using the ROC curve, with the MINI scale serving as a reference. With this analysis, different decision levels were established for various cut-off points. The cut-off point established the total score value based on the positive presence of hypomania. In addition, Student's *t*-test was used to compare 2 independent samples and the chi-squared test, corrected for continuity, was used to contrast proportions. The results of the main variables were described with 95% confidence intervals. The comparisons were performed with bilateral contrasts, with levels of significance established as equal to or lower than 0.05.

Results

The distribution of participants in each diagnostic category was as follows: 31 participants diagnosed with BP

Table 1 Sociodemographic data.

Variable	Total (n = 128)		Bipolar disorder (n = 31)		Major depression (n = 57)		General anxiety disorder (n = 15)		Control group (n = 25)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	42.2	12.5	41.5	12.8	41.1	11.5	43.3	15.1	45.1	13.1
			No.	%	No.	%	No.	%	No.	%
Area										
Emergency			49	38.0	1	3.2	33	56.9	8	53.3	7	28.0
MHC			54	41.9	4	12.9	25	43.1	7	46.7	18	72.0
SSU			15	11.6	15	48.4	0	0	0	0	0	0
BPU			11	8.5	11	35.5	0	0	0	0	0	0
Sex										
Male			50	38.8	14	45.2	20	34.5	4	26.7	12	48.0
Female			79	61.2	17	54.8	38	65.5	11	73.3	13	52.0
Place of birth										
Rural			16	13.8	3	9.7	7	15.2	2	14.3	4	16.0
Urban			100	86.2	28	90.3	39	84.8	12	85.7	21	84.0
Education level										
Primary			16	12.5	4	12.9	6	10.5	5	33.3	1	4.0
Secondary			67	52.3	14	45.2	28	49.1	6	40.0	19	76.0
University			45	35.2	13	41.9	23	40.4	4	26.7	5	20.0
Socioeconomic level										
Low/lower middle			17	15.0	3	10.0	7	15.6	4	30.8	3	12.0
Middle			80	70.8	21	70.0	30	66.7	7	53.8	22	88.0
Upper middle/upper			16	14.2	6	20.0	8	17.8	2	15.4	0	0

BPU: bipolar disorder unit; MHC: mental health centre; SSU: short-stay unit.

(30 BP-I and 1 BP-II), 57 with MD and 15 with AD. The control group consisted of 25 participants. Table 1 gives the sociodemographic characteristics of the sample, as well as the scores on the scale for each of the subgroups. The possible relationship between scores on the HCL-32 scale and the sociodemographic characteristics of the sample was analysed. The only statistically significant differences found were in the inverse relationship between the HCL-32 scores and 3 factors: age, patients born in rural environments and low socio-economic and cultural level.

The results concerning clinical stability of the sample through scores on the HRSD and YMRS scales are shown in Table 2. Patients from the major depression group obtained higher scores on the HRSD scale, while higher scores on the YMRS scale corresponded to the BP group. The modified CGI-BP scale was applied to assess the clinical stability of the patients during the 6 months before the study, with the results indicating a general condition between normal and slightly ill on each of the subscales for most subjects.

Discriminative capacity of the scale was analysed for bipolar disorder by ROC curve (Fig. 1). Discriminative capacity for the HCL-32 scale was assessed with the ROC curve, using the positive diagnosis of manic and hypomanic episodes–according to the MINI scale–as a reference or the gold standard. The ROC curve found allowed us to identify the sensitivity and specificity values for each decision level or each cut-off point on the HCL-32 scale. The cut-off point established a level of reference on the HCL-32 scale for screening hypomania. The area under the curve was 0.65 CI 95% (0.55–0.75), which indicates a low-moderate discriminative capacity.[29]

Table 3 shows the sensitivity and specificity results for each cut-off point and the hypomanic prevalence results among patients in the depression group.

Table 2 Clinical stability of the sample.

Scale	BP		Depression		General anxiety		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hamilton	4.9	5.20	15.1	4.74	10	2.75	4.6	1.99
Young	9.2	10.10	3.3	2.18	2.3	1.99	1.7	1.77
HCL-32	21.8	5.05	16.7	4.53	13.40	6.06	13.5	6.12

Table 3 Prevalence of hypomania in depression group.

HCL-32 cut-off point	Sensitivity	Specificity	Prevalence of hypomania in depression group
14	77.6 (64.9, 90.3)	37.35 (26.3–48.4)	74.1%
15	71.4 (57.8, 85.1)	45.78 (34.5–57.1)	67.2%
16	59.2 (44.4, 73.9)	55.4 (44.1–66.72)	51.7%
17	55.1 (40.2, 70.1)	57.8 (46.6–69.1)	48.3%

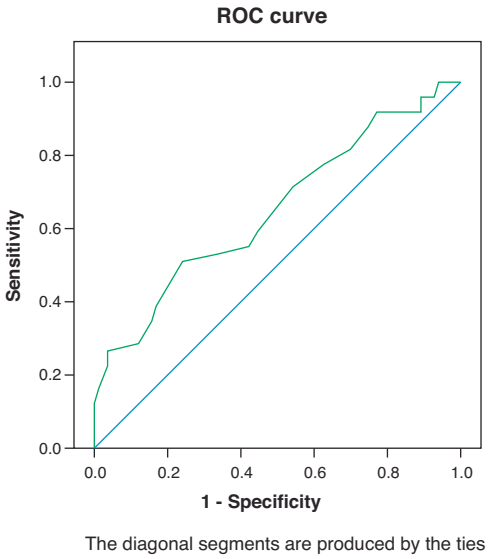

Figure 1 ROC curve representative of the usefulness of the HCL-32 scale for hypomania screening. Area under the curve 0.65 CI 95% (0.55–0.75).

The best cut-off point was 15, with sensitivity and specificity values of 71.43 and 45.78%, respectively, and positive and negative predictive values of 43.75 and 73.08%, respectively. With this cut-off point, a hypomania prevalence of 67.2% was obtained among patients with an MD diagnosis.

The possible relationship between scores on the HCL-32 scale and the IPDE was analysed by means of Spearman's rank correlation coefficient. No statistically significant differences were found in the IPDE scale results between the different groups. The results obtained did not show correlation between the HCL-32 values and abnormal personality traits.

Discussion

In our sample, the area under the ROC curve is low-moderate, considering the confidence intervals previously cited.[29] This means that the HCL-32 scale did not seem to have adequate psychometric properties for the diagnosis of hypomanic episodes in patients with a previous diagnosis of depression. Nevertheless, the HCL-32 is an instrument for screening hypomania in patients with a previous diagnosis of unipolar depression, thus requiring high sensitivity values. The data obtained for each cut-off point, according to what is shown in Table 3, correspond to a position in the area under the curve (AUC) between 0.58 and 0.82, which means a low-moderate discriminative capacity.[29] If we compare the previous studies (Table 3), we find AUC values close to those obtained in the studies from Angst et al.[28] and Rybakowski et al. (2009), with an AUC of 0.75. In turn, the Vieta et al. (2006) and Forty et al. (2007) studies obtained superior AUC levels (AUC 0.82). Considering these data, as well as the low specificity and positive predictive values, we believe the HCL-32 to be an applicable instrument in screening for hypomania. However, to reduce the percentage of false positives and obtain an appropriate diagnosis, it would be necessary to complement the evaluation with a more specific instrument. The cut-off point of 15 possesses the best psychometric properties for this objective, with a sensitivity of 71.48% and a specificity of 45.78%. The corresponding PPV to the cut-off point at 15 is 43.75% with a 95% CI (32.25–55.25) and the NPV is 73.08% with a 95% CI (60.06–86.09).

If we use this cut-off point, 67.2% of the total sample score 16 or more points, meaning that more than half of the patients in the study have had or are having a hypomanic episode. This is in agreement with the results of previous studies stating that the prevalence of BP increases to 40% among psychiatric patients.[31]

In Table 4, the results of our study were compared to the main articles published with the application of the HCL-32. Most of the studies established a cut-off point at 14,[14,24,28] although Forty et al. (2007)[30] placed it higher (20 points) in theirs.

In the Meyer et al.[32] study, the possible history of hypomania in 2 populations (German and Swedish) was examined. The authors reflected that 11.4% of the German sample and 4.7% of the Swedish sample fulfilled criteria for ''bipolarity.'' The mean score on the HCL-32 for subjects who probably had hypomanic episodes in the past was 17.82 in the German population and 17.05 in the Swedish population.

Upon analysing the results of all the studies, the sensitivity value for our cut-off point (71.43%) was lower than in the Angst et al.,[28] Vieta et al.,[14] and Carta et al.[31] studies, but slightly higher than in the Forty et al. (2007)[30] study. Regarding specificity, our figure (45.78%) was similar to that in the Angst et al.[28] and Carta et al.[31] studies, but it did not reach the high figures reflected in the Vieta[14] and Forty (2006)[30] studies.

Nevertheless, the cut-off point chosen (15) had good capacity for screening patients previously diagnosed with both types of BP, given that the percentage of subjects with more positive diagnoses of hypomania, according to the HCL-32, occurs in the BP-I group (87.1%).

Table 4 Results of main published studies performed with HCL-32.

Study	Cut-off point	Gold Standard	Sensitivity and specificity	Prevalence of hypomania	BP diagnosis (HCL-32)	Sample type
Angst et al. (2005)	≥14	MDQ	80 and 51%	N/A	N/A	Psychiatric population
Vieta et al. (2006)	≥14	MDQ	85 and 79%	26.3% depression group, 7% control	84.5% BP (64.5% BP-I)	Psychiatric population
Carta et al. (2006)	8 10 12	MDQ	90 and 42% 90 and 47% 80 and 54%	N/A	N/A	Psychiatric population
Meyer et al. (2007)	17.82[a] and 17.05[b]	DSQ/BDII	N/A	Beck Test: 0–13 points: 10.3%[a] 14–19 points: 27.8%[a] ≥20 points: 66.7%[a]	No BP population	General population
Forty et al. (2007)	≥20	BDI/ASRM	68 and 83%	17.2% in depression group	75% classified with BP	Psychiatric population
Rybakowski et al. (2009)	≥14	MDQ	N/A	37.5% (43.9% resistant to treatment)	No BP population	Psychiatric population
Present study (2010)	≥16	MINI	71.43% and 45.78%	67.2% in depression group, 36% control	87.1% classified with BP	Psychiatric population

[a] German population.
[b] Swedish population.
ASRM: Altman Self-Rating Mania Scale; BDI: Beck Depression Inventory; DSQ: Depression Screening Questionnaire; MDQ: Mood Disorder Questionnaire; MINI: Mini-International Neuropsychiatric Interview.

In reference to this, it should be pointed out that our study had an even better capacity to confirm the BP diagnosis than previous studies.[14,30]The group with the second-highest prevalence of hypomania was the MD group, in which 67.2% of them scored 16 points or more, a considerably higher figure than in previous studies.[14,24,30] Nevertheless, high rates of BP prevalence have been described (between 30 and 61%) in diagnoses that were initially MD.[7,16,19–25]

Likewise, the prevalence closest to that found in our study was in the Meyer et al.[32] study. The authors divided the German sample into 3 groups according to levels of intensity by using the Beck Depression Inventory: low level (0–13 points), medium level (14–19 points) and moderate level ($\geq$20 points). According to the results obtained, hypomania was detected in 66.7% of the subjects from the most severe group.[32]

Another important fact in our study was the prevalence found of hypomanic episodes in the AD (26.7%) and control (36%) groups, which had percentages higher than those from a study with similar methodology.[14] Nevertheless, literature shows that in the primary healthcare population, between 20 and 30% of the patients who present anxious or depressive symptoms may have BP.[33]

The disparity between the results obtained, regarding some of the previously mentioned studies could be explained by methodological differences.

Firstly, in previous studies, the population was homogenous and psychopathologically stable. With the exception of the Meyer et al.[32] study, which was carried out in the general population, the rest of the studies involved a population in a psychiatric environment.[14,24,28,30,32] Specifically, in the Vieta et al.[14] study, the entire population came from mental health centres, there were no changes in treatment during the months previous to inclusion in the study and the scores on the YMRS and HRSD scales were lower than in our study. Our population was at a severe and unstable psychopathological level and came from different environments. In the groups from the emergency and in-hospital units, the scores on the HCL-32 were, overall, higher. The prevalence figures increased from those found in other studies, thus being more similar to the studies where the HCL-32 was used with a more severe psychiatric population.[32] Although Angst et al.[28] concluded that the scale could be used as a screening instrument even in patients with active affective symptomatology, it seems that this circumstance would limit generalisation of the results.

Secondly, several studies used the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) as a diagnostic interview.[14,28,32] Instead, we applied the MINI. Despite having demonstrated moderate validity in comparison to the SCID in multiple languages,[34–36] the MINI is a diagnostic instrument designed for application in primary healthcare and other non-psychiatric environments. Using different diagnostic interviews might have caused differences between the results that we obtained and those described in previous studies.

Thirdly, most previous studies used the MDQ scale[14,24,28,32] as a reference test, a questionnaire specifically for mood disorders. Instead, we used a general diagnostic interview in our study: the MINI. This action may have made the specificity values lower than those in previous studies.

It should be emphasised that our study was carried out by resident physicians and physicians specialised in psychiatry, with training in the application of different scales. Likewise, the population used was divided not only by diagnosis but also by different environments, which contributed to a better interpretation of the data obtained. Given that the HCL-32 scale is a self-administered instrument and contains questions of a retrospective nature, we believe that the clinical state of the patients could have conditioned their perception of their own state of health.

Our study had limitations as well. The most relevant was the use of DSM-IV criteria for clinical diagnosis. As is known, recent studies suggest that the DSM-IV diagnostic criteria for BP-II are highly specific but not very sensitive[22]; this problem extends to diagnostic instruments developed after the release of DSM-IV. On the other hand, symptoms of hypomania and cyclothymia tend to be more difficult to diagnose than those of mania. Consequently, many patients on the bipolar spectrum receive a diagnosis of depression.[37,39] This way, in the BP group, only type II patients could be recruited according to DSM-IV criteria. In reality, however, according to the HCL-32 results, 67.2% of the patients diagnosed with MD could really have been diagnosed with BP-II. Therefore, the true number of BP-II patients is much higher than that diagnosed by clinicians, which justifies both this study and the use of the HCL-32 in clinical practice.

The issue of correctly diagnosing BP-II is important because many studies show that treatment for type II bipolar disorder is not initiated until 10 years after the onset of the illness.[17] This delay is largely due to the depressive episodes that appear at the onset of the illness, which are typically diagnosed as unipolar depression. In addition, patients with bipolar disorder often do not seek treatment during hypomanic episodes, given that this state is rarely perceived as pathological and is typically associated with functional improvement.[8,16,38] The results of the 2000 survey carried out in the U.S. by the National Depressive and Manic-Depressive Association[40] revealed that 69% of those with bipolar disorder were initially misdiagnosed (60% with major depressive disorder).

As we have previously commented, the data obtained by the AUC reflect a low-moderate discriminative capacity.[29] Although the studies have demonstrated that the HCL-32 is a tool designed to detect hypomanic symptoms in patients diagnosed with MD, it is not an appropriate scale for distinguishing between type I and type II bipolar disorder.[14,28] Most patients diagnosed with BP-I are going to achieve high scores on the scale because it assesses their hypomanic symptomatology as well as the repercussions of this symptomatology on different areas of patient life. On the other hand, BP-I is easier to detect than type II given that it is clinically more severe and also because it may present hypomanic episodes. In conclusion, the purpose of the scale is its usefulness in discriminating between BP and unipolar depression, limiting the under-diagnosis of BP-II.

Given the results obtained, we can highlight 2 conclusive aspects:

The HCL-32 is a detection instrument that is very sensitive but not very specific.

The HCL-32 is preferably applicable to patients with mood disorders that are psychopathologically stable and not severe at the moment of completing the scale.

For these reasons, future research needs to develop more specific measuring instruments for hypomanic symptoms with the objective of detecting, with more validity, those subjects who have experienced hypomanic episodes throughout their lives.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of Data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interests

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Randomized trial of clozapine vs. risperidone in treatment-naïve first-episode schizophrenia: Results after one year

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ABSTRACT

In first-episode patients with psychosis, clozapine may be potentially valuable as an initial treatment seeking to limit early on clinical and cognitive deterioration. Nevertheless, until recently its restricted use has limited the study of this possibility. Our research group is developing a non-commercial, multicentric and open label study on the differential efficacy between clozapine and risperidone in first-episode schizophrenia. In this paper, we present the results related to clinical variables after a one-year follow-up. So far, we have recruited 30 patients diagnosed with schizophrenia or schizophreniform disorder with illness duration of less than two years. The patients had not received any previous treatment and they were randomized to treatment with clozapine or risperidone. Our results indicate that on average, patients on clozapine adhered to their original treatment for a longer time period than patients on risperidone. By last observation carried forward (LOCF) analysis, patients on clozapine and risperidone displayed similar clinical improvements, although marginally greater improvements in positive and total symptoms scores were found in the clozapine group. At the 12-month point we observed a marginal improvement in negative symptom scores in patients on clozapine. Subjective secondary effects, as measured with the Udvalg for KliniskeUndersøgelser (UKU) scale, correlated negatively with negative symptoms at follow-up. Our data, although preliminary, suggest that clozapine may have a slightly superior efficacy in the initial year of treatment of first-episode treatment-naïve patients with schizophrenia, and this can be explained for the most part by greater adherence to this treatment.

1. Introduction

Most patients with schizophrenia present cognitive and socio-occupational impairment (Cook and Razzano, 2000; Modestin et al., 2003; Sharma and Antonova, 2003; Priebe, 2007), especially at illness onset (Mason et al., 1996). Early intervention studies failed to provide firm results in favor of a determined drug that targets cognitive and socio-occupational impairment prevention (Crossley et al., 2010; Crespo-Facorro et al., 2012). The possibility of using clozapine as a first option treatment in the initial stages of schizophrenia has been proposed long ago (Angst et al., 1971; Hofer et al., 2003; Woerner et al., 2003; Shaw et al., 2006) looking to avoid a supposed "toxicity" of the psychosis with the pharmacological treatment that better reduces the severity of psychotic symptoms (Green and Schildkraut, 1995; Agid et al., 2010). However, the past and current limitations on its use have hampered a full exploration of this alternative (Kolivakis et al., 2002).

We are only aware of one study in which first-episode patients with psychosis received clozapine without ever being treated with any other pharmacological treatment (Lieberman et al., 2003). In this seminal work, researchers compared clozapine and chlorpromazine for the duration of 52 weeks with a prospective, randomized and double-blind approach. Subsequently, the sample was tracked for nine years (Girgis et al., 2011); resulting in greater time in remission with clozapine that was not observed after one year follow-up or in the long-term. The sample was recruited in China, with certain unusual characteristics for our environment, such as: the prolonged duration of the hospitalizations, the late age-onset, the massive acceptance of inclusion and the adherence to treatment. For all of this, it might be interesting to replicate these findings in our setting.

With our present work we aimed towards examining if first-episode patients with psychosis, initially treated with clozapine, evolved more favorably than patients treated with a drug usually

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prescribed in these cases in our setting, such as risperidone. This paper is a communication of the results after the first year of a two-year follow-up design, in which neuropsychological and neuroimaging aspects will also be taken into account in further analyses.

2. Materials and methods

2.1. Framework

The study was carried out in Madrid and the patients were recruited from the area of influence of the 12 de Octubre Hospital, along with the Jiménez Díaz Foundation, Infanta Cristina Hospital and Gregorio Marañón Hospital. The ethical boards of these institutions approved the study. Since the use of clozapine was beyond its regular indication we designed a clinical trial approach authorized by the Spanish Agency of Medicine and Sanitary Products (AEMPS) (registered in the clinical trials data base of the European Medicines Agency as EUDRACT No.: 2006-002000-34). This clinical trial was developed without any commercial interests, and completely financed from public agencies: the Social Security's Health Research Fund and the Ministry of Health and Social Policy, the Advanced Therapies and Transplants National Agency.

2.2. Participants

The patients were included after written acceptance of the corresponding informed consent form. The inclusion criteria were as follows: (i) diagnosis of schizophrenia or schizophreniform disorder (according to DSM-IV criteria), with less than two years of evolution and without any previous treatment; (ii) absence of any other psychiatric disorder (Axis 1 or focal neurological signs); (iii) absence of psychotropic drugs one month before the study commencement, or antidepressants in the three months prior to inclusion; (iv) the absence of cranial trauma or infection of the central nervous system; (v) absence of drug dependency, including alcohol but, with the exception of nicotine and caffeine; and (vi) age below 35 years in males and 40 years in females.

From a total of 53 contacted patients, 33 (62.2%/21 males) agreed to inclusion. Three patients (two of them with risperidone) were excluded during follow-up for not evolving to a diagnosable schizophrenia disorder (delusional disorder, manic-depressive disorder with psychotic symptoms, and psychosis due to cocaine). Out of the 30 remaining patients, equally and randomly distributed to each drug therapy, seven patients (five of them on risperidone) abandoned the study without further explanation, and three patients (two from the risperidone group) were excluded for an absence of response and intolerance to treatment.

A total of six patients switched treatments during follow-up of the study. Two patients agreed to switch from risperidone to clozapine at weeks 3 and 5 because of manifest lack of improvement. Another two agreed to switch to clozapine at month 8 because they failed to adhere to risperidone and relapsed, the lack of adherence being secondary to intolerance. Two cases agreed to switch from clozapine to risperidone at months 8 and 9 after they failed to adhere to clozapine and relapsed. Data of these cases were only used in the last observation carried forward (LOCF) analyses within the group of the original drug.

2.3. Procedure and tools of assessment

After signing informed consents, the patients who met the inclusion criteria were randomly assigned a treatment of risperidone or clozapine. Upon acceptance, the treatment was assigned according to arrival order of the patients, i.e., even cases were assigned to the clozapine arm and odd cases to the risperidone arm, without allocation concealment. This study seeks to assess results in real treatment conditions. Therefore, even though patients were assessed according to protocol, they maintained regular clinical attention as usual in their corresponding mental health centers. In most cases the protocol included two and a half weeks of hospitalization and a follow-up on outpatient basis; made up of appointments with the psychiatrist, health-care programs and psychoeducational support.

For clinical assessment, we employed the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987)), and the Udvalg for KliniskeUndersøgelser (UKU) Side Effects Rating Scale (Lingjaerde et al., 1987); applied at weeks 1, 2, 3, 4, 6, 8, 10 and 12, and months 6, 12, 18 and 24. The dosage of the treatment was prescribed according to the patient's situation as usual in clinical practice (started at 12.5 mg a day, maximum dosage of 900 for clozapine; started at 2 mg, maximum dosage of 10 for risperidone). The mean dosage employed at week 12 was 5.22 (sd 0.97; range: 4–6) for risperidone, 226.66 (sd: 97.95; range: 100–400) for clozapine; and after one year: 5.43 (sd: 1.51; range: 4–8) for risperidone and 220.45 (sd: 112.26; range: 25–350) for clozapine.

We monitored weight, electrocardiogram, control of lipids and glycemia at baseline and week 12 (they would be re-assessed by month 24). Patients treated with clozapine followed standard blood-cell count protocol.

Patients were excluded from the study for the following reasons: not evolving to a diagnosable schizophrenia disorder, withdrawal of consent, non-fulfillment of treatment, follow-up protocol violation, pregnancy, important adverse occurrences (defined according to the "Norms of Good Clinical Practice", of the Spanish Agency for Drugs and Health Products AEMPS (AEMPS, 2008)) or therapeutic failure (defined as an increase of 50% of the total PANSS scores with respect to baseline, with scores higher or equal to "Moderate" (=4) in the items of the positive subscale; with a duration of more than two weeks) during follow-up.

2.4. Statistics

Baseline demographic, clinical and metabolic parameters were compared between clozapine and risperidone treated patients by Mann–Whitney U-test or X^2-test, when appropriate.

In order to test differences in efficacy between clozapine and risperidone in first-episode patients, we compared the outcomes in both patients groups as follows:

First, we analyzed the differences between groups (clozapine and risperidone) in number of drop-outs and treatment switches (X^2 tests), and the time from inclusion to drop-out in weeks (Mann–Whitney U tests).

Second, for within and between group comparisons of clinical efficacy (i.e., differences between baseline and follow-up) we used the data obtained in the LOCF of each case. The percent of change between baseline and LOCF (positive, negative, general and total PANSS scores) was calculated and compared between clozapine and risperidone treated patients by Mann–Whitney U tests. Additionally, we assessed the significance of changes within each group for positive, negative, general and total PANSS scores between baseline and LOCF by Wilcoxon tests.

Third, we repeated these comparisons in the patients still in treatment after 12 months (i.e., between baseline and 12-month scores). These comparisons were carried out with Mann–Whitney U tests (between-group differences in percent of change), and Wilcoxon tests (within-group changes).

Since side effects of the trial drugs might explain changes in negative symptoms, we investigated if the differences in clinical response. To do so, we defined two scores derived from the UKU: "motor" (M) (sum of severity scores for dystonia, rigidity, hypokinesia, hyperkinesia, tremor and achatysia) and "subjective"

Table 1
Demographic and clinical values at baseline.

	Clozapine (n = 15)	Risperidone (n = 15)
Age	24.5 (5.2)	24.4 (5.3)
Sex (male to female)	12:3	9:6
School years	12.6 (3.5)	12.1 (3.7)
Socioeconomic level	2.7 (0.6)	2.7 (0.6)
Caucasian	12:3	11:4
Alcohol (antecedents of use)(yes/no)	5:10	4:11
Alcohol (active abuse)	1	2
Cannabis (antecedents of use)	5:10	4:11
Cannabis (active abuse)	0	1
Cocaine*(antecedents of use)	4:11	2:13
Cocaine (active abuse)	1	1
Family antecedents	5:10	6:9
DUP (months)	7.5 (5.8)	12.3 (31.1)

* Significant between-group difference p = 0.05 (Mann–Whitney U test).

(SUB) (sum of severity scores for concentration, asthenia, somnolence, memory, excessive sleep, emotional indifference, and depression). We compared the severity of those factors between groups, and assessed the significance of the correlation of the corresponding UKU factor (i.e., by the time of the LOCF and after 12 months of treatment) with the symptom difference between baseline and follow-up by Spearman's rho test. For each factor, individual UKU scores were also compared within (difference between baseline and follow-up for each treatment arm) and between groups (LOCF scores for clozapine vs. risperidone).

Finally, we assessed the significance of metabolic changes in each group by non-parametric tests. Weight, cholesterol, triglycerides and glycemia levels were compared at baseline, and the percent of change was compared at follow-up between groups.

The study was designed to reproduce the usual treatment conditions, to a feasible extent. In order to achieve this, when a patient did not tolerate or still worsened in the early weeks with the corresponding treatment, it could be switched to the other if she/he accepted the change. Then, the case was ascribed to the original drug for final assessments (considering the scores from the LOCF before switching).

3. Results

3.1. Baseline data

There were no significant differences in sex or ethnic distribution, age, parental socioeconomic level, school years or metabolic values (weight, glycemia, triglycerides and cholesterol) between treatment groups (i.e., clozapine vs. risperidone; Table 1). There were no significant differences in past illicit drug use, except for a more frequent history of cocaine use in clozapine-treated patients. The differences in duration of untreated psychosis (DUP) between both groups did not reach statistical significance.

There were no significant differences in baseline clinical scores between patient groups, as shown in Table 2.

3.2. Time on treatment

The total rate of protocol discontinuation was 53.3%.

Patients initially assigned to clozapine remained on this treatment for a significantly longer period of time (41.1, sd 15.9 weeks) than those initially assigned to the risperidone arm (23.3, sd 20.1 weeks; U = 58, z = 2.44, p = 0.015).

Upon reaching the end of the 12th month, the number of cases with the same treatment prescribed initially (including drop-outs and switches) was higher for clozapine (9 out of 15) than for risperidone (5 out of 15). However, this difference was not statistically significant ($\chi^2 = 1.13$, df = 1, p = 0.13). If we consider adherence to treatment after one year as the outcome variable, the number needed to treat to benefit (NNT) is 4.16.

3.3. Clinical response

3.3.1. LOCF

As shown in Table 2, clinical changes with both drugs were similar, although the improvement was marginally better in the clozapine group by the time of the LOCF in positive (U = 72, z = 1.65, p = 0.10; Table 2, Fig. 1) and total scores (U = 74, z = 1.61, p = 0.10).

In the corresponding within group comparisons:

- Patients on clozapine significantly improved from baseline in positive (mean change −14.4, sd 7.4, z = −3.62, p < 0.001), general (mean change −17.3, sd 12.4, tz = −3.53, p < 0.001) and total (mean change −35.5, sd 26.6, z = −3.52, p < 0.001) PANSS scores (Table 2).
- Risperidone-treated patients significantly improved from baseline in positive (mean change −9.5, sd 7.21, z = −2.84 p = 0.004) and total (mean change −17.1 sd 27.7, z = 2.13p = 0.03) PANSS scores.

3.3.2. 12-month comparisons

In these comparisons, there were no significant differences in the percent of change between clozapine (n = 9) and risperidone (n = 5) treated patients that never switched from their original treatment (Table 2).

The within-group comparisons showed that:

- The clozapine group (n = 9) displayed a significant decrease in positive (mean change −17.3, sd 5.3, z = −2.67, p = 0.008), general (mean change −22.7, sd 10.3, z = −2.67, p = 0.008) and total (mean change −48.0, sd 24.7, z = −2.66, p = 0.008) scores, as well as a marginal decrease (mean change −8.2, sd 10.3, z = −1.66, p = 0.09) in negative symptom scores.

Table 2
Clinical values (PANSS scores) at baseline and follow-up in each group; scores from the last observation carried forward and the subset of patients surviving one year assessment. In each cell of the follow-up, mean group values and mean values of the percent change with respect to baseline are displayed. Positive values in the percent change correspond to improvement (higher baseline scores) and negative values to worsening. Side effect scores are also shown (UKU "motor" and UKU "subjective"; see text and Table 3 for individual UKU scores).

	Clozapine			Risperidone		
	Baseline (n = 15)	LOCF/% (n = 15)	12 months/% (n = 9)	Baseline (n = 15)	LOCF/% (n = 15)	12 months/% (n = 5)
Positive	25.2 (4.8)	10.3 (4.0)/56.5 (22.1)[a,b]	8.8 (3.2)/65.3 (12.5)[b]	23.2 (5.7)	13.6 (7.1)/39.1 (31.5)[b]	8.8 (2.6)/62.8 (15.0)[b]
Negative	19.2 (9.4)	15.60 (6.4)/−0.2 (59.0)	12.4 (6.3)/24.8 (49.3)[c]	16.6 (8.2)	17.8 (7.7)/−15.7 (56.7)	16.8 (7.0)/−12.4 (56.7)
General	42.4 (8.3)	25.1 (7.7)/38.2 (23.5)[b]	21.3 (4.3)/49.7 (14.2)[b]	39.6 (12.4)	30.8 (13.7)/17.6 (43.9)	22.2 (6.7)/39.2 (21.3)[b]
Total	86.6 (17.3)	43.0 (13.8)/38.2 (25.2)[a,b]	47.73 (17.2)/50.7 (18.8)[b]	79.5 (22.3)	62.3 (27.1)/19.4 (35.3)[b]	51.3 (17.0)/38.5 (23.2)
UKU-EP		0.4 (0.8)	0.4 (0.9)		0.2 (0.5)	0.3 (0.7)
UKU-SUB		3.2 (2.1)	3.3 (2.0)		2.9 (3.7)	2.6 (3.3)

[a] Marginally larger decrease in patients on clozapine as compared to risperidone (percent of decrease): p < 0.10, (U tests for independent samples).
[b] Significant change within groups (p < 0.05).
[c] Marginal change within groups (p < 0.10).

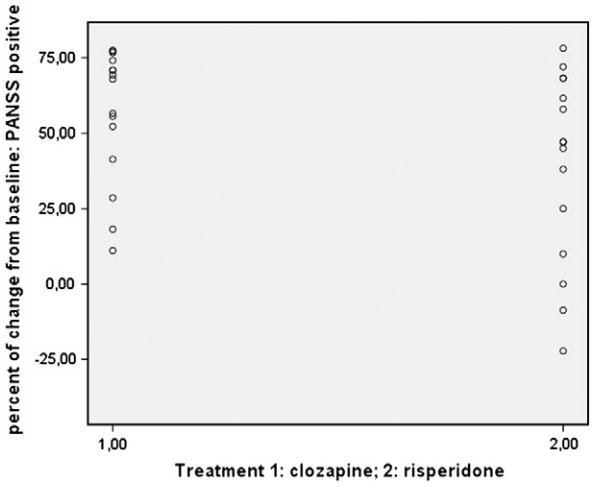

Fig. 1. Scatterplot showing the individual differences in positive PANSS (LOCF) in all patients depending on their initial treatment. Positive values represent improvements.

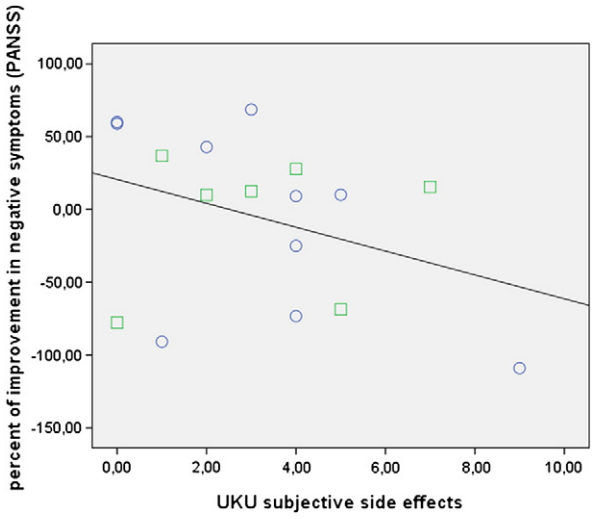

Fig. 2. Association between severity of subjective side effects measured with the UKU (see text) and improvement in negative symptom scores measured at one year. Patients with risperidone are shown as squares and with clozapine as circles. Two cases initially treated with clozapine but switched to risperidone are included in this comparison.

- The same comparisons for the risperidone group (n = 5) displayed a significant decrease in positive (mean change −15.8, sd 6.0, z = −2.03, p = 0.04) and general (mean change −15.2 m sd 9.7, z = −2.02, p = 0.04) symptoms, and a non-significant increase in negative (mean change −0.4, sd 9.52, z = −0.27, p = 0.78) PANSS scores.

Table S1 shows clinical scores in the cases in which the treating psychiatrist switched the treatment due to lack of response or intolerance.

3.3.3. Relation to UKU scores

There were no significant differences in UKU scores at 12 months or by the time of the LOCF (Table 2). In both groups, asthenia and somnolence were significantly more severe at LOCF than at baseline. In the clozapine group, concentration deficit and increased sleep time were also more severe at LOCF. In the between group comparisons, only increased sleep time was marginally more severe in the clozapine group (U = 49.5, z = 2.34, p = 0.087; Table 3).

We found a significant inverse association between subjective UKU scores and negative (Spearman's rho = −0.65, p = 0.02), general (Spearman's rho = −0.70, p = 0.01), and total (Spearman's rho = −0.71, p = 0.009) symptom improvement at 12 months (Fig. 2). That association was also significant in both risperidone and clozapine treated patients considered alone (Fig. 2).

Table 3
Individual UKU scores at LOCF in each treatment group. Significant increases from baseline (Wilcoxon test, p < 0.05) are shown in each column. Only a marginally significant difference between groups was detected for increased sleep time in the clozapine group (p = 0.087).

	Clozapine	Risperidone
Dystonia	0 (0.0)	0 (0.0)
Rigidity	0.70 (0.25)	0 (0.0)
Hypokinesia	0.20 (0.41)	0 (0.0)
Hyperkinesia	0.13 (0.51)	0.90 (0.30)
Tremor	0 (0.0)	0 (0.0)
Achatysia	0.13 (0.51)	0 (0.0)
Concentration deficit	0.53 (0.74)*	0.36 (0.81)
Asthenia	0.47 (0.64)*	0.36 (0.67)*
Somnolence	0.53 (0.64)*	0.36 (0.67)*
Memory alteration	0.20 (0.41)	0.09 (0.30)
Depression	0.13 (0.35)	0.18 (0.45)
Increased sleep time*	0.40 (0.51)*	0 (0.0)
Emotional blunting	0.33 (0.62)	0 (0.0)

3.4. Metabolic comparisons

Both groups showed significant weight gain from baseline to endpoint, as well as increase in glycemia and cholesterol (Table S2). Nevertheless, these changes were not significantly different between groups.

4. Discussion

We used clozapine without life-threatening adverse effects in first-episode patients with schizophrenia or schizophreniform disorder and no previous treatment. The preliminary data presented here suggest that clozapine may have a slightly superior efficacy than a standard treatment (risperidone) for such cases, specifically in relation to treatment adherence. Nevertheless, clinical changes by LOCF were similar with both drugs.

We found greater adherence to clozapine. Patients on clozapine tended to show better adherence to treatment for a longer period of time than those on risperidone. Furthermore, the relatively low NNT in reference to adherence to treatment after one year in favor of clozapine supports this notion. This greater adherence would pragmatically associate to greater efficacy. The demonstrated need to adhere to treatment (Leucht et al., 2012) and the overwhelming relation between drop-outs and relapse in schizophrenia (Ascher-Svanum et al., 2006; Haro et al., 2006; Novick et al., 2010), support the consideration of adherence to antipsychotic treatment as a pragmatic indicator of effectiveness (Lieberman et al., 2005).

The higher tendency to adhere to original treatment with clozapine vs. risperidone resembles Lieberman's group results with clozapine vs. chlorpromazine, for short (Lieberman et al., 2003) as well as long-term outcome (Girgis et al., 2011). Nevertheless, our sample's global drop-out rate is higher (53.33%) than those from the former of these studies (18.75% during the first year), which could be attributed to the different variables compared (CPZ vs. Ris) or to the different sociocultural and health care intervention frameworks. However, our data comply with relapse rates from other schizophrenia studies on pharmacological treatment (between 30% and 75% based on follow-up) (Canas et al., 2013) and more specifically, with similar studies in the first stages of the disease (Coldham et al., 2002; Subotnik et al., 2011).

Although there were no significant differences between groups, the clozapine group showed a marginal improvement in negative

symptoms at the 12-month period whilst in the risperidone group a not significant worsening in these symptoms was instead observed. Moreover, we found a relation between the intensity of secondary effects (called "Subjectives") and higher scores in Negative and Total Scores. Since available data indicate that antipsychotics are not efficacious against primary negative symptoms (Blanchard et al., 2011; Miyamoto et al., 2012), our data suggest that secondary negative symptoms may increase significantly with risperidone. Clozapine may not contribute to the increase of secondary negative symptoms as much as risperidone, as supported by phase 2 of the CATIE study (McEvoy et al., 2006). However, risperidone actively generates secondary non-motor negative symptoms (Artaloytia et al., 2006), which we would be gathering as subjective secondary effects (UKU-SUB) at the same time as negative symptoms (PANSS-N), and could favor less adherence to treatment in patients.

Greater adherence and a tendency to improve with clozapine may be observed because of better tolerance towards this treatment, which allows for more time on the treatment; or because of greater efficacy in treating psychopathology, which facilitates adherence to treatment. In any case, it seems that time on treatment is key in the patient outcome. In fact, we did not find any differences in the improvements obtained in patients that adhered to the original treatment after 12 months; although, the very small number of risperidone cases reaching that point did not allow for an adequate comparison.

Some cases used illicit drugs, but a primary causative role for these drugs in the psychotic process was reasonably discarded. Clozapine patients had used cocaine more frequently. However, this is indeed a bad prognostic factor and, therefore, unlikely to explain the slightly better outcome with this drug. There were no significant differences in other prognostic factors (family antecedents, other substance use, DUP). A greater sample is needed to explore if these factors influence the response to clozapine in our patients.

Our work has the basic limitation of the design, since the restriction to clozapine use renders double-blinding virtually impossible. Otherwise, numbers are low, due to the inherent difficulties of recruiting and treating first psychotic episodes for this kind of protocol (Robinson, 2011) and the effort made to discard patients without a likely progression to schizophrenia. A broader sample may possibly result in more significant differences in the outcomes. Our results are still provisional until the completion of the samples' follow-up in numbers and time-frames. Therefore, they do not clearly confirm the general hypothesis of an improvement in patients' disease progression when treated with clozapine. However, some data are directed towards this line of thought.

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Contributors

J. Sanz, T. Palomo and V Molina designed the study and drafted the manuscript; D. Taboada performed neurocognitive assessments; and J. Sanz, S. Ovejero and C. del Alamo recruited and clinically assessed patients. All authors have approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.07.003.

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Prolonged social withdrawal disorder: A *hikikomori* case in Spain

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Abstract

Background: The Japanese term *hikikomori* means literally 'to be confined'. Social withdrawal can be present in severe psychiatric disorders; however, in Japan, *hikikomori* is a defined nosologic entity. There have been only a few reported cases in occidental culture.

Material: We present a case report of a Spanish man with prolonged social withdrawal lasting for 4 years.

Discussion: This is a case of prolonged social withdrawal not bound to culture, as well as the second case of *hikikomori* reported in Spain. We propose prolonged social withdrawal disorder as a disorder not linked to culture, in contrast to *hikikomori*.

Conclusion: Further documentation of this disorder is still needed to encompass all cases reported in Japan and around the world.

Keywords

Hikikomori, social withdrawal, social isolation

Introduction

The Japanese term *hikikomori* (literally meaning 'to be confined') makes reference to a syndrome commonly seen in Japan that is related to prolonged social withdrawal that cannot be explained by another psychiatric disorder. This prolonged social withdrawal was first described by Kasahara in 1978 as 'withdrawal neurosis' or *taikyaku shinkeishou* (Teo, 2010). Later in 1986, Kitao coined the term *hikikomori* in the academic setting (Furlong, 2008); however, it wasn't until 1998 that Saito defined the term *hikikomori* as a free-standing syndrome with distinct symptoms (Furlong, 2008; Teo & Gaw, 2010).

Even though *hikikomori* is not included in the principal diagnostic criteria, authors using the term in their studies have coincided when characterizing the principal symptoms, for example, prolonged isolation at home lasting for more than 6 months (Furlong, 2008; Koyama et al., 2010; Nagata et al., 2013; Teo, 2010; Teo & Gaw, 2010; Wong, 2009). In addition, authors such as Furlong (2008) and Wong (2009) indicated absence from work, training or school as another characteristic symptom. This absence is referred by Wong as 'status zero'. Finally, Saito (as mentioned by Teo, 2010) characterized *hikikomori* as individuals who do not maintain interpersonal relationships, excluding close family members.

Although other characteristics have been noted by various authors, they have not been consistently mentioned across the literature. For example, Furlong (2008) stated that a subject may leave his or her house for small shopping trips. These trips tend to occur only during the early hours of the morning or late at night when they are less likely to be seen by others. Some subjects attempt to hide their condition by leaving their homes in the morning, as if leaving for work or school, only to spend hours on the train or aimlessly walking in areas where they will not be recognized (Furlong, 2008). García-Campayo, Alda, Sobradiel and Sanz Abos (2007) indicated that although many of these subjects do not fall within the diagnostic criteria for psychiatric symptoms (neither Axis I nor II), they may still present traits of paranoid personality and social introversion. In addition, aversive or traumatic childhood experiences were frequently found among the *hikikomori*, such as being bullied or shun by peers (Teo, 2010). In 2003, the Japanese Ministry of Health, Labor, and Welfare, using the scientific literature, defined *hikikomori* as a lifestyle centered at home with no interest in attending work or school that

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persists for at least 6 months and whose symptoms cannot be explained by another mental disorder, for instance, schizophrenia or mental retardation (Teo, 2010).

Sufficient epidemiologic data on the *hikikomori* does not exist due to the relative novelty of the syndrome. However, there does seem to be an agreement on the prevalence of the syndrome in Japan: approximately 0.5% of Japanese households and 1.2% of the population aged 20–49 years have experienced *hikikomori* in their lifetime. The majority of *hikikomori* cases have been identified in Japan, although cases have also been reported in Korea (Lee, Koo, Kim, & Lee, 2001), Oman (Sakamoto, Martin, Kumano, Kuboki, & Al-Adawi, 2005), Spain (García-Campayo et al., 2007) and recently in the United States (Teo, 2013) in a case associated with depression. The average age of onset of *hikikomori* is 22.3 years with an average duration of 1 year (Koyama et al., 2010). Various authors agree that a greater prevalence exists in males (Kondo et al., 2013; Koyama et al., 2010).

Currently, there is no agreement on the possible triggers of voluntary isolation without a previous psychiatric history. Some authors (Furlong, 2008; Teo, 2010) have focused on sociocultural explanations in an attempt to explain possible triggers, such as, the vast structural changes the Japanese culture has experienced in the past decades due to globalization. Another proposal by Kato et al. (2012) reflects upon the theory of *amae*, created by Takeo Doi. *Amae* is a Japanese concept used to describe dependent behaviors, much like a child's dependence on his or her parents. The child acting *amae* can be selfish, begging or indulgent, all while securely knowing that the parent will forgive all. This phenomenon could be an indirect promoter of *hikikomori*, an indicator of why parents accept their children staying at home. In the opinion of some authors (Niiya, Ellsworth, & Yamaguchi, 2006), *amae* could be a universal concept not found solely in the Japanese culture.

The debate within the scientific community is currently centered on the concept of *hikikomori* as a free-standing diagnostic criterion. Some past studies have considered *hikikomori* as a symptom of another disorder (Gariup, Parellada, García, & Bernardo, 2008; Kondo et al., 2013; Malagón, Alvaro, Córcoles, Martín-López, & Bulbena, 2010; Nagata et al., 2013), while others define *hikikomori* as a syndrome independent of another diagnosis (Kato et al., 2012). Some authors argue that it is solely a culture-bound syndrome found exclusively in Japan (Teo & Gaw, 2010); however, Teo (2013) and Kato et al. (2012) have recently noted the possibility of *hikikomori* existing in other cultures outside of Japan.

In this article, we present a case of *hikikomori* detected in a short-term hospitalization unit in Madrid, Spain, the second case reported in our country (García-Campayo et al., 2007). Finally, we propose a model that allows us to explain the occurrences of these cases outside of the Japanese culture.

Clinical case

L.J. is a 25-year-old male who was involuntarily admitted to our short-term hospitalization unit (Fundación Jiménez Díaz) for evaluation of a suspected psychotic disorder. The patient spent 4 years in his room, leaving only occasionally late at night to obtain hashish (one joint per day). His daily activity was limited to the confined space of his room where he spent the day watching movies, playing video games and chatting online.

The patient maintained good personal hygiene and order within his room. He stopped attending school at age 16 without completing the third year of Secondary Studies and has not worked since age 18. Although he is currently without a group of friends, his father (with whom he lives) describes him as previously being a social person and having good relationship with his peers. His medical history includes psychological treatment at the age of 12 due to the divorce of his parents and sporadic consumption of cannabis and alcohol during his adolescence. The patient also has a simple phobia of needles. The father has a history of alcohol abuse.

L.J. has exhibited school problems since childhood, although he did have a structured group of friends. Since the age of 12, following the separation of his parents, the patient has had various changes in residence. During adolescence, he suffered from bullying by fellow classmates at school. During this time, he left school and began consuming cannabis. At age 18 years, he began having odontological problems of unknown origin that were complicated by his fear of needles. As a result, he developed cavities and gingivitis that required the removal of almost all of his teeth by age 20 (simple extractions of teeth: 17, 16, 15, 14, 13, 24, 25, 26, 27, 38, 37, 36, 35, 34, 42, 43, 44, 45, 46, 47 and 48). This loss and his final change in residence coincided with the patient's progressive isolation and social withdrawal.

During a psychopathological evaluation, the patient exhibited fluid and coherent discourse. No disturbance in form or content of thought was observed. Hallucinations and distortion of perception were not observed. The patient relates his isolation with the shame he feels in his interpersonal relationships due to his lack of teeth. He explains he did not get dental prostheses implanted due to his 'fear of needles'. He resisted going to dental appointments for the removal of his teeth and was obligated by his father to go.

At the moment of discharge, the main diagnosis was 'prolonged social withdrawal syndrome'. Secondary diagnoses were 'Harmful consumption of cannabis' and 'Simple phobia of needles'.

For the differential diagnosis, four mental disorders were taken into account: schizophrenia, major depression disorder, social phobia and amotivational syndrome. First, schizophrenia was ruled out due to the fact that clinical psychosis was not observed during inpatient stay nor did

family members report previous psychotic symptoms. No negative symptoms were observed that would lead us to think of simple schizophrenia. Depression was also considered but no alterations of mood were observed, although the patient has referred to feeling sad on occasions because of his isolation. In relation to social phobia, the patient does not report any anxiety symptoms during social reunions or anticipatory ones. No characteristic symptoms of social phobia were observed during hospital admission. Finally, amotivational syndrome was also ruled out since the patient has maintained interests and has remained active within his home. He has also maintained self-care.

The following intervention and treatment was offered: therapeutic counseling was provided to the patient's father to assist in decreasing reinforcement of L.J.'s avoidance behavior. Also, sertraline 50 mg/day was prescribed as a long-term treatment; in addition, lorazepam 1 mg was prescribed as needed to help with the patient's phobia of needles during his dental appointments.

One month after discharge, L.J. was given an appointment to check evolution. He had begun to progressively leave his room and home. He was looking for a dentist to commence dental prostheses, as well as attending driving school. Millon Clinical Multiaxial Inventory, Third Edition (MCMI-III, Spanish version; Cardenal & Sánchez, 2007) was administrated with no significant results.

Discussion

We present the case of a Spanish young adult male with prolonged social withdrawal lasting more than 4 years. The clinical presentation of the patient matches the descriptions given by Japanese psychiatry of *hikikomori*; however, in the case of our patient, symptoms are not bound to culture. The patient's culture of origin, which can be defined as a typical occidental culture in a European Mediterranean country, does not influence the presentation and maintenance of prolonged social isolation. On the contrary, the Spanish culture encourages social contact and favors interpersonal relationships outside of the home. Since Spanish culture differs from Japanese culture, we propose that the prolonged social withdrawal is based on the individual characteristics of our patient and not on culture.

The individual characteristics that define the clinical presentation of social withdrawal in this patient are the following: phobic personality traces, including a simple phobia of needles and avoidant behavior of social situations due to the shame caused by his dental problem. As mentioned before, other personality traces, such as paranoid (García-Campayo et al., 2007), social introversion (García-Campayo et al., 2007) or dependent traces (Kato et al., 2012) are related to *hikikomori*.

This is the second case of *hikikomori* reported in Spain (García-Campayo et al., 2007). Other cases have also been reported outside of Japan in Oman and Korea (Lee et al., 2001; Sakamoto et al., 2005). In addition, Kato et al. (2012), who surveyed psychiatrists from different countries around the world, stated that typical cases of *hikikomori* exist not only in Japan but also in other parts of Asia, Australia and the United States.

In the literature, multiple terms are used to refer to this condition, for instance, acute social withdrawal, prolonged social withdrawal, severe social withdrawal and social isolation. The term 'prolonged social withdrawal' has been previously used by Kondo et al. (2013) to refer to the general condition of *hikikomori* seen in Japan. Tateno, Park, Kato, Umene-Nakano, and Saito (2012) proposed that the term *hikikomori* could be used to describe severe social withdrawal in the setting of a number of psychiatric disorders.

In order to create a separation between the culture-bound *hikikomori* and cases such as ours, we believe the term 'prolonged social withdrawal disorder' is useful. This terminology helps not only to differentiate from the typical *hikikomori* observed in Japan but also includes all clinical presentations observed outside of Japan.

According to Pies (2009), a disorder must meet one of the following criteria to be considered a 'specific disease entity':

- A pattern of genetic transmission.
- Etiology, pathophysiology and/or pathologic anatomy of the syndrome must be reasonably well known.
- The course, prognosis, stability and response to treatment of the syndrome must be relatively predictable and consistent across different populations.

Under these conditions, we can assume that *hikikomori*, as a non-culture bound disorder, can exist as a comprehensive etiopathological explanation. As is mentioned above, individual characteristics presented in this case can explain the prolonged social withdrawal of our patient.

Teo (2010) emphasizes that current nosology in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) may not adequately capture the concept of *hikikomori.* Furthermore, the diagnostic criteria for *hikikomori* proposed by Teo and Gaw (2010) for the *DSM, Fifth Edition* (*DSM-V*) are entirely applicable to cases of prolonged social withdrawal not bound to culture. In fact, these authors do not make reference to culture factors in their criteria. Taking these criteria into consideration, we propose a clinical grouping for prolonged social withdrawal:

1. Prolonged social withdrawal disorder, as a distinct disorder not culture-bound.
2. Prolonged culture-bound social withdrawal disorder or *hikikomori*.

Prolonged social withdrawal disorder secondary to an organic disease or to another mental disorder (e.g. schizophrenia, agoraphobia and personality disorders) that directly justifies the clinical presentation should be excluded.

Conclusion

The Western literature has described various cases of prolonged social withdrawal phenomenologically similar to cases of *hikikomori* described in Japan. We propose a grouping encompassing clinical cases beyond those connected to culture, although the vast majority of cases are reported in the Japanese culture. Therefore, prolonged social withdrawal disorder could be utilized to distinguish between cases linked to culture from those linked to individual factors. Further documentation of cases exhibiting prolonged social withdrawal is needed, as there exist few documented cases outside of Japan, as well as to allow the use of terminology for this disorder at a universal level.

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PLOS ONE

RESEARCH ARTICLE

Development of a Web-Based Clinical Decision Support System for Drug Prescription: Non-Interventional Naturalistic Description of the Antipsychotic Prescription Patterns in 4345 Outpatients and Future Applications

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Abstract

Purpose

The emergence of electronic prescribing devices with clinical decision support systems (CDSS) is able to significantly improve management pharmacological treatments. We developed a web application available on smartphones in order to help clinicians monitor prescription and further propose CDSS.

Method

A web application (www.MEmind.net) was developed to assess patients and collect data regarding gender, age, diagnosis and treatment. We analyzed antipsychotic prescriptions in 4345 patients attended in five Psychiatric Community Mental Health Centers from June 2014 to October 2014. The web-application reported average daily dose prescribed for antipsychotics, prescribed daily dose (PDD), and the PDD to defined daily dose (DDD) ratio.

Competing Interests: The authors have declared that no competing interests exist.

Results

The MEmind web-application reported that antipsychotics were used in 1116 patients out of the total sample, mostly in 486 (44%) patients with schizophrenia related disorders but also in other diagnoses. Second generation antipsychotics (quetiapine, aripiprazole and long-acting paliperidone) were preferably employed. Low doses were more frequently used than high doses. Long acting paliperidone and ziprasidone however, were the only two antipsychotics used at excessive dosing. Antipsychotic polypharmacy was used in 287 (26%) patients with classic depot drugs, clotiapine, amisulpride and clozapine.

Conclusions

In this study we describe the first step of the development of a web application that is able to make polypharmacy, high dose usage and off label usage of antipsychotics visible to clinicians. Current development of the MEmind web application may help to improve prescription security via momentary feedback of prescription and clinical decision support system.

Introduction

Since their first introduction in the 1950s, antipsychotic medications have been used to treat a growing array of conditions. While first approved as treatment for schizophrenia [1], their use has rapidly extended to other disorders. Currently, FDA-approved uses of typical antipsychotics include schizophrenia, bipolar disorder, psychotic disorders in general, agitation, hyperactivity, Tourette syndrome, generalized nonpsychotic anxiety, and severe behavioural problems [2]. The applicability of these drugs increased only further with the introduction of atypical antipsychotics [3]. These are now approved to treat conditions that range from autism to major depressive disorder (MDD) [4].

Nonetheless, off label use of antipsychotic drugs is still an extended practice. Prescribing antipsychotic drugs to treat unapproved conditions and employing excessive doses are two of the most common examples. In particular, antipsychotics have been regularly used to treat behavioural symptoms in elderly patients with dementia, despite conflicting evidence to support it [5]. In fact, the percentage of patients with FDA-unapproved disorders taking antipsychotics in the US has been estimated to range from 60% to 83% [6,7], with an estimated cost in 2008 of $6.0 billion [6].

Finally, many patients are treated with two or more antipsychotic drugs in combination, although its effectiveness remains to be demonstrated [8,9]. Antipsychotic polypharmacy refers to the co-prescription of more than one antipsychotic drug for an individual patient [10]. In outpatient settings, antipsychotic polypharmacy is somewhat less frequent when compared to inpatient populations, possibly due to lesser illness severity. However, in a large cohort in the US consisting of outpatients from three different health care settings, Sun et al. [11] reported that approximately one fifth of those with psychotic disorders were under a treatment schedule consisting of more than one antipsychotic drug. In Canada, Procyshyn et al. [12] reported an antipsychotic polypharmacy prevalence of 25.7% in outpatients. Furthermore, in a European outpatient setting, Novick et al. [9] reported polypharmacy in approximately one third of the patients, with a tendency for a slight increase during a one year follow up. A recent review further reported that among adults, off label prescription consisted of 40 to 75% of all antipsychotic prescriptions [13]. Antipsychotic polypharmacy is common. Evidence of efficacy

however, is limited to small randomized controlled clinical trials, case reports, and individual clinician experience. At the same time, antipsychotic polypharmacy has been associated with an increased risk of metabolic syndrome [14], higher healthcare costs [15], and possibly mortality [16].

Over the last decade, medical prescription security has been supported by the emergence of electronic health records (EHRs) and clinical decision support systems (CDSS) that facilitate portability and processing of pertinent health information related to pharmacological treatment [17]. This has helped monitor prescription patterns that include off label use, polypharmacy and high dosage. Inter-institutional EHRs are used to further increase efficiency in medical services and provide complete and accurate medical information across providers in different institutions [18]. CDSS are made possible by digitalization of clinical data. Their purpose is to improve clinical management, methodological contributions, sensitivity and simulation tools in order to evaluate the clinical impact of the prescription decisions. The emergence of electronic prescribing devices with decision support systems significantly reduces error rates [19]. They also reveal an important source of epidemiological insight about how treatment is prescribed and taken, although these are extremely expensive and are not widely implemented. However, current EHRs often fall short of delivering readily available, compiled and tailored medical knowledge regarding the patient to the clinician [20]. The availability of handheld computing provides the opportunity to implement many of these gains to institutions where e-prescribing systems are not yet accessible. The increasing availability of smartphone technology permits the gathering of naturalistic data that can be processed immediately and provide instantaneous decision making assistance to clinicians.

A pioneer project in the 1980s programmed drug monitoring systems to identify evidence-based medication practices in 11 New York State Institutions for Mental Health and Developmental Disabilities. The results of the study showed that the surveillance techniques improved prescribing practices [21]. EHRs are now used routinely and are a major source of structured data. In a naturalistic, observational, retrospective, non-interventional study, Gavirina et al. [22] were able to describe prescription habits in a sample of 1700 patients suffering from schizophrenia. The data were gathered from computerized or e-medical records that were registered in the electronic medical record and implemented in all centers of the network that performed the assessment.

However, these systems present some limits that are related to the methodology of such studies; observational studies based on retrospective analysis of EHR data. For example routine practice data are collected for billing or institutional purposes. The re-use of these data to advance clinical research can be challenging [23]. The timing, quality, and comprehensiveness of clinical data are often not consistent with research standards [24]. Accuracy (correctness) of data relies on correct and careful documentation, which is often difficult to perform though most EHR used in routine. Furthermore, due to the architecture of traditional EHR, data cannot be processed instantaneously to deliver a CDSS, which requires a double task of de-identification of the data, and statistical analysis out of the software core. Most studies describing antipsychotic habits use retrospective methods [25]. By doing so, researchers and clinicians miss the opportunity to process gathered data in the moment and use them for CDSS purposes. The use of electronic records for decision support at a clinical level is still not widely reported. EHRs are usually commercial software only accessible from computers having wired connection. This characteristic excludes systematic assessment of outpatients that are treated by primary care services or those that are hospitalized out of the mainstream care services.

Taking into consideration the strengths and pitfalls of each of these monitoring strategies, we developed a web application that is able to adapt to any common routine follow-up strategy and research protocol in medicine. The growth and popularity of mHealth apps (health-related

software applications), their ease of use and their cost of development compared to traditional software make them particularly suitable for the task of prescription monitoring.

Our Hypothesis was that a web application developed for this study may be able to describe clinician prescriptions. The objective of this study was to describe, via the Memind web-application, the prescription patterns of antipsychotics in a naturalistic outpatient setting in five Psychiatric Community Mental Health Centers in Madrid, Spain. We focused primarily on off label uses and antipsychotic polypharmacy.

Materials and Methods

Study setting

Four thousand nine hundred and seventy-five patients received psychiatric care in five Psychiatric Community Mental Health Centers (Moncloa Mental Health Center, Arganzuela Mental Health Center, Infanta Elena Hospital, Valdemoro Mostoles Hospital, Hospital 12 de Octubre Hospital) part of the Psychiatry Department of Fundacion Jimenez Diaz in Madrid, Spain, during the study period (from June 2014 to October 2014). This department is part of the National Health Service and provides medical coverage financed by taxes to a catchment area of 800,000 people. Fifty-five clinicians of the Memind study group participated in the patient recruitment process. Outpatients were assessed during routine medical visit by these clinicians. The clinician also created a profile in the MEmind web application for each patient that met the inclusion criteria and agreed to participate.

Patient inclusion and exclusion criteria

Inclusion criteria were either male or female outpatients, aged 18 or older, who gave written informed consent. Participants were excluded from the study if they were under the age of 18, incarcerated, under guardianship, enrolled in other trials, or were in emergency situations where their state of health did not allow for obtaining written informed consent.

Material

The web application was specifically developed for Android and OSX Smartphones, Tablets and the Mac and PC versions of Mozilla firefox and Google Chrome. It is available in three languages (English, French, Spanish). The web application has two distinct interfaces. The "electronic health record" view is designed for use by health care providers during clinical rounds and medical or nursing visits. It has been designed to cover all the data acquired during a standard psychiatric evaluation, including sociodemographic, diagnostic and pharmacological treatment information. Furthermore, it is based on commonly stored information in mental health management. A large customizable choice of relevant scales can be added by the care provider to the basic evaluation. The patient view was also developed and will allow patients to be monitored with ecological momentary assessment (EMA) tools in future studies. Patient had no access to this function for the present study.

Three different user profiles exist: 1) for patients; 2) for caregivers/family; and 3) for mental health professionals. For the purposes of this study we only used the mental health professional profile (Fig 1). During this study, patients did not have access to the web application. If they agreed to participate to the study, they only agreed to allow their clinician to enter their personal data into the MEmind web application. The patients were still treated as usual.

Each patient was identified by a numeric code that ensures patient anonymity. This code is encrypted in the database that remained the same throughout all contact with patients cared for during the study.

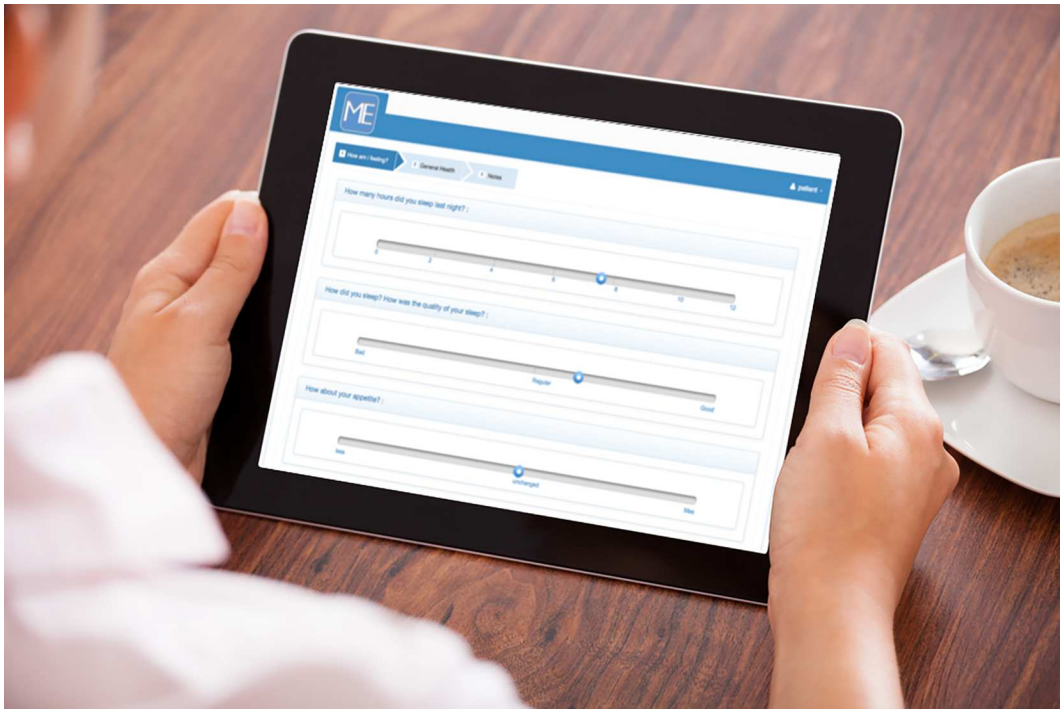

Fig 1. The MEmind web application as viewed from an OSX tablet.

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Baseline assessment

For this study, variables collected for each patient profile were sex, age, diagnosis and treatment. Clinical diagnoses were made by psychiatrists or clinical psychologists, coded according to the ICD-10 [26] for mental disorders, and entered manually into the MEmind web-application. Diagnoses were assigned by the clinician, not automatically done by the application. Allocation of information was done by the clinician via the clinician interface of the web application.

Outcomes measures

Pharmacological treatment was registered with our web tool and then classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD)[27]. We calculated the average of daily dose prescribed for antipsychotics (N05A ATC code), Prescribed Daily Dose (PDD), and the PDD to DDD ratio. Although ATC classification includes lithium and antipsychotics under the N05A code, for the purpose of this study we only included antipsychotics. In order to compare dosages of the various antipsychotics we used a fixed unit of measurement based on dividing the prescribed daily dose (PDD) by the defined daily dose (DDD). A PDD/DDD ratio greater than 1.5 was defined as excessive dosing [12]. We performed double verification of the results using the SSPS version 22.0 package.

Ethical considerations

The research was in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Institutional Review Board and granting agency. All the participants provided written informed consent, after the complete description of the study. Previously, the research protocol was approved by the local (Fundacion Jimenez Diaz) Ethics Committee.

Table 1. Prevalence of psychiatric disorders (n = 4975).

Psychiatric disorder	N (4975)	%
F0-F09 Organic, including symptomatic, mental disorders	85	2.0
F10-F19 Mental and behavioural disorders due to psychoactive substance use	314	7.2
F20-F29 Schizophrenia, schizotypal and delusional disorders	574	13.2
F30-F39 Mood [affective] disorders	1221	28.1
F40-F48 Neurotic, stress-related and somatoform disorders	1956	45.0
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors	176	4.1
F60-F69 Disorders of adult personality and behaviour	475	10.9
F70-F79 Mental retardation	41	0.9
F80-F89 Disorders of psychological development	10	0.2
F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	74	1.7
F99-F99 Unspecified mental disorder	49	1.1

doi:10.1371/journal.pone.0163796.t001

Results

Diagnoses and sample characteristics

Out of the 4975 outpatients that received psychiatric care during study period, 4345 agreed to participate to the study. The distribution of psychiatric disorders attended in our outpatient units is shown in Table 1, and the distribution of the most common disorders according to age and gender is shown in Table 2.

Out of our total sample, 3640 patients had one psychiatric diagnosis, with anxiety and related disorders (F40-F49) being the more frequent diagnoses. The rest of the patients showed a co-morbid condition. Antipsychotics were used in 1116 patients (25% of total patients), 829 (74%) in monotherapy and 287 (26%) in poly-therapy (for detail see Table 3).

Antipsychotic pattern use

Concerning diagnoses, as a simple diagnosis or comorbidity, out of the 1116 patients in which antipsychotics were prescribed, 44% of them (486 patients) were used in patients with

Table 2. Age and gender distribution of most common psychiatric disorders (n = 4354).

		Schizophrenia and other psychoses (n = 574; 13.2%)	Mood disorders (n = 1221; 28.1%)	Neurotic. stress related and somatoform disorders (n = 1956; 45.0%)	Personality disorder (n = 475; 10.9%)	Total (n = 4345)
Age n (%)	18–35 years	132 (23%)	146 (12%)	424 (21.7%)	114 (24.1%)	890 (20.5%)
	35–50 years	232 (40.5%)	329 (27%)	733 (37.5%)	208 (43.6%)	1517 (34.9%)
	50–65 years	160 (27.8%)	446 (36.5%)	561 (28.7%)	119 (25.1%)	1304 (30%)
	>65 years	50 (8.6%)	300 (24.5%)	238 (12.2%)	35 (7.3%)	634 (14.6%)
	p-value	<0.001	<0.001	<0.001	<0.001	
Gender n (%)	Female	377 (65.6%)	855 (70.0%)	1330 (68.0%)	275 (57.9%)	1621 (62%)
	Male	197 (34.4%)	366 (30.0%)	626 (32.0%)	200 (42.1%)	2724 (37.3%)
	p-value	<0.001	<0.001	<0.001	0.024	

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Table 3. Antipsychotic monotherapy and polypharmacy according diagnosis (n = 1116).

Diagnosis		Patient with specific diagnostic N (%)	Antipsychotic use	Antipsychotic monotherapy	Antipsychotic polypharmacy
One diagnosis	F0-F09	44 (1.0%)	26 (2.3%)	23 (2.8%)	3 (1%)
	F10-F19	111 (2.6%)	26 (2.3%)	24 (2.9%)	2 (0.7%)
	F20-F29	476 (11.0%)	462 (41.4%)	305 (36.8%)	157 (54.7%)
	F30-F39	966 (22.2%)	268 (24%)	204 (24.6%)	64 (22.2%)
	F40-F49	1630 (37.5%)	82 (7.3%)	78 (9.4%)	4 (1.4%)
	F50-F59	101 (2.3%)	9 (0.8%)	9 (1.1%)	0 (0%)
	F60-F69	203 (4.7%)	69 (6.1%)	60 (7.2%)	9 (3.1%)
	F70-F79	22 (0.5%)	13 (1.2%)	9 (1.1%)	4 (1.4%)
	F90-F99	87 (2%)	7 (0.62%)	7 (0.8%)	0 (0%)
Comorbidity	F0-F09 + F30-F39	15 (0.3%)	11 (1%)	8 (1%)	3 (1.0%)
	F10-F19 + F20-F29	23 (0.5%)	23 (2%)	11 (1.3%)	12 (4.2%)
	F10-F19 + F30-F39	33 (0.8%)	12 (1%)	8 (1%)	4 (1.4%)
	F10-F19 + F40-F49	36 (0.8%)	5 (0.4%)	5 (0.6%)	0 (0%)
	F10-F19 + F60-F69	23 (0.5%)	9 (0.8%)	7 (0.8%)	2 (0.7%)
	F20-F29 + F40-F49	13 (0.3%)	12 (1%)	10 (1.2%)	2 (0.7%)
	F20-F29 + F60-F69	13 (0.3%)	12 (1%)	6 (0.7%)	6 (2.1%)
	F30-F39 + F40-F49	47 (1.1%)	8 (0.7%)	6 (0.7%)	2 (0.7%)
	F30-F39 + F50-F59	17 (0.4%)	1 (0.1%)	0 (0%)	1 (0.3%)
	F30-F39 + F60-F69	83 (1.9%)	32 (2.9%)	22 (2.7%)	10 (3.5%)
	F40-F49 + F40-F49	73 (1.7%)	10 (0.9%)	10 (1.2%)	0 (0%)
	F40-F49 + F50-F59	32 (0.7%)	1 (0.1%)	1 (0.1%)	0 (0%)
	F40-F49 + F60-F69	73 (1.7%)	18 (1.6%)	16 (1.9%)	2 (0.7%)
	Other combinations	224 (5.2%)	0 (0%)	0 (0%)	0 (0%)
	TOTAL	4345	1116 (26%)	829 (19%)	287 (6.6%)

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schizophrenia and related disorders, 28% (309 patients) in affective disorders, 13% (140 patients) in personality disorders, and 136 (12%) in anxiety and related disorders. It is interesting to note that 14 patients with schizophrenia and related disorders did not receive antipsychotics (Table 3).

Out of the 1116 patients using antipsychotics, 1475 antipsychotic prescriptions were made. Out of the 829 patients (74%) using an antipsychotic as a monotherapy, antipsychotics were the only therapy used for 185 (185/829, 22%) of them. The most common combination of antipsychotics with another psychotropic drug was with antidepressants (in 109 patients). Antipsychotics were used in polypharmacy regimen in 287 patients (26%). In 151 patients, the combinations were only used with other antipsychotics.

Table 4 shows the different antipsychotics prescribed, ATC/DDD classification and doses employed in our clinical practice. It is important to note that antipsychotics used in an excessive dosing were long-acting paliperidone and ziprasidone.

The proportion of polypharmacy for every antipsychotic and the dose used when antipsychotics were used alone or in combination are showed in Tables 5 and 6.

Discussion

Main findings

In this study, we described a method to perform naturalistic prospective data gathering regarding prescription habits via a web-based application available from a smartphone or any other Internet-connected wireless device. This observational study was the first step of the development of CDSS that may help care providers to better monitor their prescriptions. We found that antipsychotics were mostly used in schizophrenia and related disorders but also in other disorders, in both approved and off label indications. Antipsychotic polypharmacy was employed in 26% of prescriptions made. Second-generation antipsychotics were mainly chosen for prescriptions (quetiapine, aripiprazole and long-acting paliperidone). Excessive dosing was only found with long acting paliperidone and ziprasidone whereas the use of low doses was relatively common. In this study, we were able to identify polypharmacy high dose and off label use in an outpatient setting. These results provide information about drug management under real conditions and highlight discrepancies between guidelines and actual practice that could guide research in new uses for drugs.

Limitations

The current study was performed in a naturalistic setting of patients treated as usual. Out of the 4975 outpatients that received psychiatric care during study period, 4345 agreed to

Table 4. Prescribed Daily Dose (PDD), and the PDD to defined daily dose ratio of antipsychotics (n = 1116).

Number of prescriptions	Drug	ATC code	DD (mg)	Median PDD (mg)	Mean PDD (mg)	PDD (mg) IC 95%	PDD/DDD
47	Amisulpride	N05AL05	400	400.00	520.21	401.63–638.79	1.30
262	Aripiprazole	N05AX12	15	10.00	12.76	11.68–13.84	0.85
88	Asenapine	N05AH05	20	7.50	9.29	8.07–10.51	0.46
3	Chlorpromazine	N05AA01	300	100.00	76.67	30.93–122.40	0.26
24	Clotiapine	N05AH06	80	40.00	37.20	31.71–42.69	0.47
65	Clozapine	N05AH02	300	280.00	287.92	254.42–321.43	0.96
16	Fluphenazine	N05AB02	1	0.89	0.89	0.72–1.05	0.89
25	Haloperidol	N05AD01	8	5.00	6.96	4.36–9.55	0.87
13	Levomepromazine	N05AA01	300	38.75	63.61	41.46–85.76	0.21
1	Levosulpiride	N05AL07	400	25.00	25.00		0.06
150	Olanzapine	N05AH03	10	10.00	9.82	8.66–10.98	0.98
104	Paliperidone	N05AX13	6	6.00	7.56	6.61–8.50	1.26
214	Long-acting paliperidone	N05AX13	2,5	3.57	4.41	4.17–4.65	1.76
1	Perphenazine	N05AB03	30	8.00	8.00		0.27
3	Pimozide	N05AG02	4	4.00	3.67	0.82–6.51	0.92
279	Quetiapine	N05AH04	400	100.00	194.35	170.76–217.95	0.49
110	Risperidone	N05AX08	5	3.00	4.15	3.51–4.79	0.83
5	Long-acting risperidone	N05AX08	2,7	3.57	3.57	1.65–5.49	1.32
1	Sertindole	N05AE03	16	4.00	4.00		0.25
2	Sulpiride	N05AL01	800	100.00	100.00		0.13
19	Tiapride	N05AL03	400	100.00	144.74	107.34–182.13	0.36
14	Ziprasidone	N05AE04	80	90.00	130.00	72.36–187.64	1.63
1	Zuclopenthixol	N05AF05	30	25.00	25.00		0.83
28	Zuclopenthixol depot	N05AF05	15	9.52	11.39	10.01–12.78	0.76

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Table 5. Proportion of antipsychotic polypharmacy compared with monotherapy (n = 1116).

Drug	ATC code	Prescriptions N (%)	Monotherapy N (%)	Polypharmacy N (%)
Amisulpride	N05AL05	47 (3.2%)	19 (40%)	28 (60%)
Aripiprazole	N05AX12	262 (17.6%)	181 (69%)	81 (31%)
Asenapine	N05AH05	88 (5.9%)	59 (67%)	29 (33%)
Chlorpromazine	N05AA01	3 (0.2%)	1 (33%)	2 (67%)
Clotiapine	N05AH06	24 (1.6%)	5 (21%)	19 (79%)
Clozapine	N05AH02	65 (4,4%)	22(34%)	43 (66%)
Fluphenazine	N05AB02	16 (1.1%)	5 (31%)	11 (69%)
Haloperidol	N05AD01	25 (1.7%)	11 (44%)	14 (56%)
Levomepromazine	N05AA01	13 (0.9%)	10 (77%)	3 (23%)
Levosulpiride	N05AL07	1 (0.1%)	0	1 (100%)
Olanzapine	N05AH03	150 (10.0%)	102 (68%)	48 (32%)
Paliperidone	N05AX13	104 (7%)	63 (61%)	41 (39%)
Long-acting paliperidone	N05AX13	214 (14.4)	118 (55%)	96 (45%)
Perphenazine	N05AB03	1 (0.1%)	1 (100%)	0
Pimozide	N05AG02	3 (0.2%)	2 (67%)	1 (33%)
Quetiapine	N05AH04	279 (18.8%)	176 (63%)	103 (37%)
Risperidone	N05AX08	110 (7.5%)	61 (55%)	49 (45%)
Long-acting risperidone	N05AX08	5 (0.3%)	4 (80%)	1 (20%)
Sertindole	N05AE03	1 (0.1%)	0	1 (100%)
Sulpiride	N05AL01	2 (0.1%)	2 (100%)	0
Tiapride	N05AL03	19 (1.3%)	15 (79%)	4 (21%)
Ziprasidone	N05AE04	14 (0.9%)	4 (29%)	10 (71%)
Zuclopenthixol	N05AF05	1 (0.1%)	0	1 (100%)
Zuclopenthixol depot	N05AF05	28 (1.9%)	5 (18%)	23 (82%)
TOTAL		1475	866 (58.7%)	609 (41%)

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participate to the study. It is likely that some patients were not asked to participate due to the supplementary burden of entering data into the MEmind web application. Furthermore, some patients did not meet the inclusion criteria or refused to participate. During the preliminary process of the study, clinicians pointed out that the monitoring of patient acceptability, including refusal and reason for refusal or agreement, would add an additional task to fulfill during the consultation. This could have altered the naturalistic setting required for the study. Another concern of clinicians was also that this monitoring would have provided information about individual performance toward recruitment process. For these reasons, patients not meeting the inclusion criteria, patients who were not asked to participate, and patients refusing to participate were considered to be "missing data". Overall, 4345 were finally included in the final analysis. Thus, data were partially or totally missing for 630 patients (12%) that were not included in the final analysis.

Type of antipsychotics used

In our practice, second-generation antipsychotics were more commonly used than classic antipsychotics, with quetiapine, aripiprazole and long-acting paliperidone representing the most prescribed antipsychotics. This prescription habit reflects how second-generation antipsychotics have become the first-line of treatment for schizophrenia because of their fewer extrapyramidal side effects [28–30].

The prevalent use of quetiapine reflects our outpatient setting with anxiety and mood disorders being the more frequent disorders. This also suggests greater approval and off label use of

Table 6. Antipsychotic doses when use in combination (n = 287).

Drug	ATC code	One antipsychotic		Two antipsychotics		Three antipsychotics		Four antipsychotics	
		N (%)	Mean PDD (mg)	N (%)	Mean PDD (mg)	N (%)	Mean PDD (mg)	N (%)	Mean PDD (mg)
Amisulpride	N05AL05	19 (2.2%)	315.79	22 (4.5%)	665.91	5 (4.7%)	720.00	1 (10%)	200.00
Aripiprazole	N05AX12	181 (21%)	11.01	71 (14.4%)	16.48	9 (8.4%)	17.22	1 (10%)	25.00
Asenapine	N05AH05	59 (6.8%)	8.01	23 (4.7%)	12.61	6 (5.6%)	9.17	0 (0%)	
Chlorpromazine	N05AA01	1 (0.1%)	30.00	0 (0%)		2 (1.9%)	100.00	0 (0%)	
Clotiapine	N05AH06	5 (0.6%)	34.00	13 (2.6%)	35.38	5 (4.7%)	48.00	1 (10%)	20.00
Clozapine	N05AH02	22 (2.5%)	248.64	40 (8.13%)	307.13	3 (2.8%)	320.00	0 (0%)	
Fluphenazine	N05AB02	5 (0.6%)	0.63	8 (1.62%)	1.05	3 (2.8%)	0.89	0 (0%)	
Haloperidol	N05AD01	11 (1.3%)	3.75	11 (2.2%)	9.34	2 (1.9%)	12.50	1 (10%)	5.00
Levomepromazine	N05AA01	10 (1.2%)	76.00	2 (0.4%)	100.00	1 (0.9%)	100.00	0 (0%)	
Levosulpiride	N05AL07	0 (0%)		1 (0.2%)	25.00	0 (0%)		0 (0%)	
Olanzapine	N05AH03	102 (11.8)	8.97	37 (7.5%)	11.96	10 (9.3%)	11.00	1 (10%)	5,00
Paliperidone	N05AX13	63 (7.3%)	6.57	31 (6.3%)	8.81	9 (8.4%)	10.67	1 (10%)	3.00
Long-acting paliperidone	N05AX13	118 (13.6%)	4.00	81 (16.5%)	4.81	15 (14%)	5.48	0 (0%)	
Perphenazine	N05AB03	1 (0.1%)	8.00	0 (0%)		0 (0%)		0 (0%)	
Pimozide	N05AG02	2 (0.23%)	2.50	1 (0.2%)	6.00	0 (0%)		0 (0%)	
Quetiapine	N05AH04	176 (20.3%)	158.45	79 (16.1%)	244.78	21 (19.6%)	309.52	3 (30%)	166.66
Risperidone	N05AX08	61 (7.0%)	3.12	41 (8.3%˚	5.30	7 (6.5%)	6.50	1 (10%)	3.00
Long-acting risperidone	N05AX08	4 (0.5%)	3.57	1 (0.2%)	3.57	0 (0%)		0 (0%)	
Sertindole	N05AE03	0 (0%)		1 (0.2%)	4.00	0 (0%)		0 (0%)	
Sulpiride	N05AL01	2 (0.2%)	100.00	0 (0%)		0 (0%)		0 (0%)	
Tiapride	N05AL03	15 (1.7%)	140.00	3 (0.6%)	150.00	1 (0.9%)	200.00	0 (0%)	
Ziprasidone	N05AE04	4 (0.5%)	65.00	7 (1.4%)	165.71	3 (2.8%)	133.33	0 (0%)	
Zuclopenthixol	N05AF05	0 (0%)		1 (0.2%)	25.00	0 (0%)		0 (0%)	
Zuclopenthixol depot	N05AF05	5 (0.6%)	9.52	18 (3.7%)	11.90	5 (4.7%)	11.43	0 (0%)	
TOTAL		866		492		107		10	

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quetiapine in recent years [30]. In this way, quetiapine could be used for generalized anxiety disorder [31], depression [32,33], insomnia [34] or dementia-related psychiatric symptoms [30,35].

Range of diagnoses where antipsychotics were used and off label use

Consistent with findings in Spain [36], in our sample, around half of antipsychotic prescriptions were made in schizophrenia and related disorders while the rest were in other diagnoses. We also found that antipsychotics were prevalently utilized for mood disorders, personality disorders and, anxiety and related disorders (F40-F49 IDC codes) with more than 50% of prescriptions used in these three categories. As mood disorders include bipolar disorder, antipsychotic use is logical and expected. It is also important to remember approved and evidence based use of second generation antipsychotics in treatment-resistant depression (29,30). For anxiety and personality disorders, mainly represented by borderline personality disorder, antipsychotic use is not approved but widespread, with evidence based results on the topic [37,38]. A minority use of antipsychotics in our sample was made by participants with substance use disorders, mental retardation or ICD codes between F0 and F09 which includes dementia. These are uses consistent with those previously reported [39,40]. Patients with schizophrenia that did not have antipsychotic medication were patients in a change in treatment process (wash out period).

Considering the prevalent use of antipsychotics, it is interesting to reflect on how within complex situations, or even just daily clinical practice, solutions may be required that sometimes do

not fit guidelines. Additionally, it is common in psychiatric practice to treat symptoms against diseases using the pharmacodynamic properties of drugs in order to guide treatment [41].

Antypsychotic polipharmacy

The 26% rate of antipsychotic polypharmacy found in our sample is consistent with rates in outpatient settings worldwide [9,11,12] and in Spain [42,43]. Guidelines accepted antipsychotic polypharmacy in cases of cross-titration, control of acute disturbances and clozapine augmentation [44,45]. As our study is a transversal observation of our sample, we cannot measure cases of cross-titration. Acute disturbances are more likely treated in an inpatient setting, so that is not a plausible explanation for our rates of polypharmacy. Concerning clozapine augmentation, we used this antipsychotic in polypharmacy in 66% of cases, but this still does not explain all the polypharmacy employed.

Interestingly, classic long acting antipsychotics were mostly used in polypharmacy, 82% of prescriptions of zuclopenthixol depot and 69% of fluphenazine, which may reflect a frequent and non-evidence based clinical practice in patients with chronic schizophrenia course [46].

Clotiapine is another classic antipsychotic more frequently used in combination (79% of prescriptions). This high rate of polypharmacy and the low dosage generally used of this drug (PDD/DDD = 0.47) probably highlights its use for its hypnotic properties rather than as an antipsychotic. Clotiapine is an antipsychotic with a rapid onset of action and a strong sedative effect, which explains its use in insomnia in psychotic and non-psychotic patients [47].

Finally, amisulpride is also used in combination (68%) more frequently than in monotherapy. It is commonly said that for amisulpride, polypharmacy is the rule rather than the exception [48]. Moreover, amisulpride may be particularly suitable for clozapine augmentation [49]. This is a probable use in our sample according to our data.

Antipsychotics dosing

According to our results, only two antipsychotics were employed at excessive dosing: long-acting paliperidone (PDD/DDD = 1.76) and ziprasidone (PDD/DDD = 1.63). This finding is consistent with previous knowledge; high doses are prevalent in hospitalized patients with schizophrenia [50,51] and less frequent in outpatient settings [52].

On the other hand, many antipsychotics were also used at low doses. This dosage use could be explained by the outpatient setting, where patients usually are in an established moment of the illness. Furthermore, antipsychotics are used in conditions other than psychosis, like insomnia in the case of clotiapine, chlorpromazine or levomepromazine, or mood and anxiety disorders or behaviour disorders in dementia, in the case of quetiapine. Special mention is needed for asenapine, an antipsychotic approved in Spain only for manic episodes in bipolar disorder. This narrow indication probably reflects its low dose usage.

Information for this study was obtained with a novel web tool, the mental state tracker MEmind. This device also has an interesting potential use in clinical research. Data collected by the provider are instantaneously transmitted to the database and made available for data mining. The system is also able to deliver alarms. In this pilot study we only made both raw data and graphic information about medical prescription available for the provider. We are currently assessing the possibility of incorporating, in the analysis, data proceeding directly from the patient that uses the EMA function of the program.

Future development and implementation

In this study, treatment related information was collected via the web-application but processed secondarily by statistical software. As a result, it would have been possible to give

instantaneous feedback to the care provider. Programs also exist that are able to alarm care providers about treatment interaction [53]. However, for the first step of the development of our web application, we decided to only monitor prescription habits and disable momentary feedback about treatment and alarm function of our web application. Alarms and feedback are part of the decision making support process [54]. By enabling this function in our web application, we probably would have faced the professional reluctance to welcome our web application in a routine clinical setting. Many studies have encountered difficulties incorporating EHRs into routine practices, especially when associated with CDSS. We are currently assessing professional acceptability of the device in order to propose a CDSS to clinicians that could be easily incorporated in their practice. Evaluating changes in routine practice caused by the use of the Memind application would also be an objective.

The objective of this study was to describe the prescription habits of antipsychotics via the Memind web-application. The Memind web application has Patient interface but this feature was not enabled for the present study. As a result patient acceptability of the application was not assessed, and neither was treatment adherence or symptom tracking using the EMA function. EMA involves repeated sampling of subjects' behaviors and experiences in real time, in their natural environment. EMA has been successfully used for real-time self-reporting of symptoms and behaviours. This feature will soon allow us to integrate data proceeding from patient self-monitoring into CDSS.

Although many EHR CDSS have yet to be developed, their performance varies largely. Approaches that foster the impact of CDSS often rely on improved alerting concerning evidence-based recommendation or drug-drug interaction. We also believe that alerting could be taken into account by implementing or refining a severity grading. For this very first step of development, we only focused on the capacity of the web application to monitor prescription [55]. However, smartphone technology gives us the opportunity to combine pharmacological insight into analysis with idiosyncratic clinical data proceeding either from medical assessment or patient. A promising challenge would be to further incorporate an alert algorithm into a clinical dimension, for example integrating it into EMA data [56].

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MEmind Study Group

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Original Paper

Ecological Assessment of Clinicians' Antipsychotic Prescription Habits in Psychiatric Inpatients: A Novel Web- and Mobile Phone–Based Prototype for a Dynamic Clinical Decision Support System

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Abstract

Background: Electronic prescribing devices with clinical decision support systems (CDSSs) hold the potential to significantly improve pharmacological treatment management.

Objective: The aim of our study was to develop a novel Web- and mobile phone–based application to provide a dynamic CDSS by monitoring and analyzing practitioners' antipsychotic prescription habits and simultaneously linking these data to inpatients' symptom changes.

Methods: We recruited 353 psychiatric inpatients whose symptom levels and prescribed medications were inputted into the MEmind application. We standardized all medications in the MEmind database using the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD). For each patient, MEmind calculated an average for the daily dose prescribed for antipsychotics (using the N05A ATC code), prescribed daily dose (PDD), and the PDD to DDD ratio.

Results: MEmind results found that antipsychotics were used by 61.5% (217/353) of inpatients, with the largest proportion being patients with schizophrenia spectrum disorders (33.4%, 118/353). Of the 217 patients, 137 (63.2%, 137/217) were administered pharmacological monotherapy and 80 (36.8%, 80/217) were administered polytherapy. Antipsychotics were used mostly in schizophrenia spectrum and related psychotic disorders, but they were also prescribed in other nonpsychotic diagnoses. Notably, we observed polypharmacy going against current antipsychotics guidelines.

Conclusions: MEmind data indicated that antipsychotic polypharmacy and off-label use in inpatient units is commonly practiced. MEmind holds the potential to create a dynamic CDSS that provides real-time tracking of prescription practices and symptom change. Such feedback can help practitioners determine a maximally therapeutic drug treatment while avoiding unproductive overprescription and off-label use.

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KEYWORDS

clinical decision-making; antipsychotic agents; software; mobile applications; off-label use; prescriptions

Introduction

From Electronic Health Records to mHealth Applications

Over the last decade, management of patients in hospitalization units has been supported by the emergence of electronic health records (EHRs) [1]. This software facilitates portability and processing of pertinent health and pharmacological treatment information [2]. These systems can support prescription practice and help practitioners determine maximally therapeutic pharmacological treatments while avoiding pitfalls such as off-label use, polypharmacy, and overly high dosages. Moreover, the emergence of electronic prescribing or e-prescribing devices with clinical decision support systems (CDSSs) has significantly reduced diagnosis and prescription error rates [3]. However, it remains difficult to extract clinically relevant information from current CDSS tools, as these data are often not tailored to the exact needs of the patient and clinician [4]. The availability of mobile phones and other handheld computers provides the opportunity to improve prescription practices in institutions where e-prescribing systems are not yet available. For example, Web-based and mobile phone–based programs permit the gathering of naturalistic data that can be processed immediately and provide instantaneous decision-making assistance to clinicians [5,6]. Overall, the appearance of these devices in medical practice has heralded the mobile health (mHealth) era, which in turn falls under the umbrella of electronic health (eHealth), where mobile devices are used to advance public health [7]. The combination of high levels of mental illness and high levels of mobile phone usage worldwide highlights the potential for mH^2 interventions (ie, mHealth mental health interventions) [8].

Wirelessly connected technologies have also increased communication and data transfer between clinicians and their patients, which further helps achieve these mHealth goals [9]. The processing of naturalistic data is especially critical given the enormous complexity of individual conditions [10]. Data mining techniques can also allow for automatic extraction of meaningful data from large clinical databases, which can help answer important treatment and outcome questions and refine best practices. Moreover, this data mining can help develop algorithms and guidelines to help care providers who require assistance [11]. These algorithms may be of particular interest to prescribers and can be used to improve the incorporation of prescription guidelines into clinical practice [12].

Challenges in Managing Psychopharmacological Treatments

However, despite these technological advances, the management of psychopharmacological treatment still grapples with many challenges. Antipsychotics are widely prescribed in psychiatric inpatient units and, as a result, off-label use is common. Although they are mostly prescribed in schizophrenia spectrum and related disorders, antipsychotics are also used off-label in a range of chronic diseases and they have been utilized as augmentation for depressive disorder [13], autism spectrum disorders [14], or off-label use, which is controversial but not uncommon [15]. For example, one study conducted across 7 provinces within Spain showed that antipsychotics were not only used in schizophrenia (22.8%) but also in other psychiatric disorders such as bipolar disorder (14.4%), depressive disorders (12.5%), personality disorders (9%), substance use disorders (1.3%), and dementia (4.5%), with 32.8% considered off-label uses [16]. Antipsychotic polypharmacy (APP) is also controversial yet quite common. APP is the use of 2 or more antipsychotics concurrently by a single patient. APP is commonly used against general clinical guideline recommendations [17]. A recent systematic review of APP prevalence between 1970 and 2009 found in a sample of 1,418,163 patients with mental disorder (82.9% with a diagnosis of schizophrenia) a median APP prevalence of 19.6% across different geographical regions, ranging from 6% to 90%, with higher median prevalence in Asia (32%) and Europe (23%) compared with North America (16%) and Oceania (16.4%) [18]. APP differs according to treatment setting, requiring more extended use in greater illness severity, such as that in inpatient settings [19,20]. In Spanish inpatient settings, APP is common with 47.1% of patients in a psychiatric hospital [21] and figures between 40% and 50% in psychiatric brief hospitalization units [22]. These studies highlight the discrepancy between guidelines and the real-world treatment. We can observe a paradigm shift in APP from discouraging all uses of polypharmacy to determining patient profiles that could benefit from polypharmacy [23]. In a naturalistic observational study, Gaviria et al [24] analyzed existing EHRs to collect data on prescription habits in a sample of 1765 patients with schizophrenia. Out of the sample of 1765 patients, 505 (28.6%) were receiving treatment with antipsychotic monotherapy, whereas 1229 (69.6%) were receiving 2 or more antipsychotics (polypharmacy). Another concern regarding antipsychotic prescription is the use of antipsychotics above their recommended doses. Overly high dosage can increase risk for adverse reactions and increases treatment cost without clear evidence of added therapeutic benefit [24]. This practice, although prevalent in clinical settings, is discouraged in clinical

guidelines [25]. These challenges highlight the importance of exploring innovative prescription monitoring methods for the field of mental health.

Toward a Mobile Clinical Decision Support System

Given the many proven benefits of EHRs for clinical practice, EHRs may also provide a possible solution to the issues that exist with antipsychotic prescription habits. Specifically, EHRs are a major source of structured data that can provide useful and ecologically valid insights into how antipsychotics are prescribed. These EHR systems, however, presented many limitations that are related to the methodology of such studies. First, conducting clinical research using data produced by EHRs can be challenging, as the timing, quality, and comprehensiveness of the clinical data often do not meet the rigorous standards of clinical research. Furthermore, owing to the architecture of traditional EHRs, data cannot be processed instantaneously to deliver a CDSS. Before delivering a CDSS, data must be deidentified as well as statistically analyzed, which has not yet been automated by software into an instantaneous process. Notably, most studies that use EHRs to describe antipsychotic habits implement retrospective methods [26]. As a result, researchers and clinicians miss the opportunity to process gathered data in the moment and use these data for clinical decision making. Finally, EHRs are usually only accessible as expensive commercial software packages, which precludes assessment of inpatients treated by institutions outside of large, mainstream health care institutions.

Web-based and mobile phone–based prescription management tools exhibit numerous advantages over these expensive, mainstream EHR software packages. Specifically, the low development cost and increasing popularity of mHealth apps (ie, health-related software applications) have made them particularly accessible across both large and small psychiatric care settings. In addition, mHealth apps often feature simple interfaces, can be used wirelessly from any location with a cell signal, and provide adequate computing power to provide CDSS capability. For the most part, these mHealth apps in mental health have been directly marketed to either consumers or small clinical practice settings. A review of mobile phone apps for schizophrenia found only 5 studies of mobile phone apps for patients with schizophrenia. All examined feasibility, and one assessed the preliminary efficacy [27]. For example, Nicholas et al [7] showed that the contents of currently available apps for bipolar disorder are not in line with practice guidelines or established self-management principles.

Taking into consideration the strengths and pitfalls of each of these strategies, our aim was to develop a Web application that could monitor prescription habits in psychiatric inpatient units. This study presents the preliminary step in the development of a CDSS. Our hypothesis was that a Web application developed for this study may be able to describe clinicians' prescriptions in a sample of inpatients. The objective of this study was to describe via the MEmind Web application the prescription habits of antipsychotics in a naturalistic inpatient setting focusing on off-label uses and APP.

The ultimate goal of this MEmind prototype is to allow physicians to provide more effective care while better adhering to clinical guidelines.

Methods

Study Design

This pilot study was a 5-month, multicenter, nonrandomized, and observational feasibility study. Participants were adults admitted in 2 brief psychiatric inpatient units (Fundación Jiménez Díaz Moncloa Hospital and Pontones Hospital, Madrid, Spain).

Setting

The 2 brief psychiatric inpatient units are part of the Department of Psychiatry of the Fundación Jiménez Díaz Hospital, which belongs to the National Health Services and provides medical coverage financed by taxes to a catchment area of ~800,000 people. A total of 4 psychiatrists are in charge of the 20 beds in each of these units. Roughly 14 nurses cover 3 work shifts in both units. Patients admitted were treated as usual. The psychiatrist in charge of the patient proposed participation in the study after verification of the inclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria were either males or females, aged 18 years or older, who were admitted to a psychiatric inpatient unit, and who gave written informed consent. Participants were excluded from the study if they were younger than 18 years, incarcerated, under guardianship, were enrolled in other trials, or were in emergency situations where their state of health did not allow for obtaining written informed consent.

Study Procedure

During their hospitalization in the psychiatric unit (PU), all patients were assessed with the MEmind Web application after giving written informed consent. The MEmind application was developed for the study by an industrial partner and is available online for download via a secure link provided to the participant via email. The application was designed to gather observational data and to perform ecological momentary assessment (EMA). It has 2 distinct views: the clinician view and the patient view. The "clinician" view is designed to be used by doctors and nurses during their clinical rounds and during their medical or nursing visits (see Figure 1, which displays the MEmind Web application). MEmind was also designed to capture all the data typically gathered during a standard medical evaluation, including sociodemographic, diagnostic, and pharmacological treatment information. MEmind's design is based on commonly stored information in mental health management. To this end, the care providers can customize the software to add a number of large relevant scales to suit their individual needs (eg, the specific needs of research vs clinical settings). At the time of discharge, we collected patients' sex, age, diagnosis, and treatment types during their stay in the psychiatric unit. As the study was performed in Spanish mental health centers, the Spanish version of the tutorials for mental health professionals was used. In addition to the clinician view, the MEmind program features a patient view that allows patients to track their

symptoms using EMA techniques. This feature was not assessed in our study. Medication compliance was not assessed in this study. For the purposes of this study, we monitored patients' diagnoses and clinicians' prescriptions. The only users who accessed the app were the clinicians who recorded their prescriptions directly into MEmind's clinician interface. Clinicians could access the Web application either from a computer or their personal mobile phone.

Clinical diagnoses and treatment prescription were conducted during hospital admission as part to routine psychiatric evaluations that incorporated data from medical records, other research assessments, and clinical interviews. All diagnoses recorded into the MEmind app were coded according to the *International Classification of Diseases, Tenth Revision*, for mental disorders alongside the data from these aforementioned psychiatric evaluations.

Figure 1. View of the MEmind Web application.

Outcome Measures

Antipsychotic medication treatments were recorded into the MEmind app and then classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD). For each patient, the treatment management function of the Web application calculated the average of daily dose prescribed for antipsychotics (N05A ATC code), prescribed daily dose (PDD), PDD 95% CI, and the mean PDD to DDD ratio. Although ATC classification includes lithium and antipsychotics under the N05A code, we chose to include only antipsychotics for the purposes of this study. To compare dosages of various antipsychotics, we used a fixed unit of measurement calculated by dividing the PDD by the DDD. A PDD/DDD ratio greater than 1.5 was defined as excessive dosing [28]. All analyses were conducted using SPSS version 22.0 (IBM Corporation).

Ethical Considerations

The research was in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the institutional review board and granting agency. All the participants provided written informed consent after the complete description of the study. Previously, the research protocol was approved by the Ethics Committee of Fundación Jiménez Díaz, Madrid.

Results

Sample Characteristics

A total of 359 patients received brief psychiatric care in the 2 psychiatric inpatient units from June 2014 to October 2014. Among them, 353 patients were evaluated with the MEmind application. Of the 6 patients who did not participate in the study, 1 patient refused to participate and 5 patients did not receive the proposal to participate. The distribution of the main psychiatric disorders according to age and sex is presented in Table 1.

Table 1. Age and sex distribution of psychiatric disorders.

Psychiatric disorder	Patients with the diagnosis, n (%)	Age, %					Sex, %		
		18-35 years	35-50 years	50-65 years	>65 years	*P* value[a]	Female	Male	*P* value[a]
Substance use disorders	79 (22.4)	19.3	47.4	33.3	0	.02	51.8	48.2	.41
Schizophrenia and other psychoses	134 (38)	28.4	37.9	24.2	9.5	.83	42.5	57.5	.79
Mood disorders	100 (28.3)	25.7	23.0	35.1	16.2	.009	54.0	46.0	.238
Personality disorders	70 (19.8)	35.4	47.9	16.3	0	.007	52.9	47.1	.505
Total (N=353)		27.3	35.5	27.3	9.8		48.7	51.3	

[a]The *P* value was calculated using the chi-square test.

Out of our total sample, 243 patients had 1 psychiatric diagnosis, with schizophrenia spectrum and related disorders being the most frequent diagnoses. Other diagnoses were comorbid diagnoses and were considered secondary to their psychotic disorder diagnoses. Antipsychotics, alone or in combination with other psychotropic drugs, were used in 217 of the 353 patients (61.5%). Of the 217 patients, 137 (63.2%) were administered pharmacological monotherapy and 80 (36.8%) were administered polytherapy (for details, see Table 2).

Antipsychotic Medication Use Pattern

The frequencies of prescription according to diagnoses, as a unique or comorbid condition, were as follows: Of the 353 patients, 118 (33.4%, 118/353) patients had a diagnosis of schizophrenia and other psychosis (F20-F29), 86 (24.3%, 86/353) had a diagnosis of mood disorders (F30-F39), 50 (14.1%, 50/353) had a diagnosis of personality disorders (F60-F69), and 33 (9.3%, 33/353) had a diagnosis of anxiety-related disorders (F40-F49; see Table 2).

Antipsychotics were prescribed to 217 patients corresponding to a total of 365 antipsychotics prescriptions. In 62 (29.2%) patients, antipsychotics were the only psychotropic drug prescribed; in 40 (18.9%) patients 1 antipsychotic was prescribed and in 22 (10.4%) patients 2 antipsychotics were prescribed. For the remaining 155 patients, antipsychotics were used in combination with other psychotropic drugs. Thus, only 18.9% of our sample were patients in a pure monotherapy antipsychotic regimen. Table 3 presents the different antipsychotics prescribed, ATC/DDD classification, and doses used in our clinical practice. The antipsychotics used in excessive doses were amisulpride, olanzapine, risperidone, and paliperidone (both their oral and long-acting injectable forms). On the other hand, levomepromazine was used in the lowest dose followed by clotiapine and quetiapine.

The antipsychotics used more frequently in APP were clozapine (81.8%), clotiapine (81.8%), and amisulpride (70.6%) through oral administration and fluphenazine (100%), zuclopenthixol acufase (100%), and zuclopenthixol depot (83.3%) through long-acting injectable forms (for details, see Multimedia Appendices 1 and 2).

Table 2. Antipsychotic medication use according to diagnosis.

Diagnosis	Patients with diagnosis, n (%)	Antipsychotic use	Antipsychotic monotherapy	Antipsychotic polytherapy
One diagnosis (n=243)				
Substance use disorders	16 (4.5)	8	6	2
Schizophrenia and other psychosis	101 (28.6)	101	62	39
Mood disorders	69 (19.5)	51	33	18
Anxiety-related disorders	24 (6.8)	5	4	1
Personality disorders	21 (5.9)	12	10	2
Rest of the diagnoses	12 (3.4)	0	0	0
Comorbidity (n=110)				
Organic disorders + mood disorders	5 (1.4)	2	1	1
Substance use disorders + schizophrenia and other psychosis	10 (2.8)	9	4	5
Substance use disorders + mood disorders	6 (1.7)	6	4	2
Substance use disorders + personality disorders	7 (2.0)	9	4	5
Schizophrenia and other psychosis + personality disorders	7 (2.0)	6	3	3
Mood disorders + personality disorders	6 (1.70)	4	2	2
Anxiety-related disorders + personality disorders	9 (2.5)	4	4	0
Other combinations	60 (17)	0	0	0
Total	353	217	137	80

Table 3. Anatomical Therapeutic Chemical classification with defined daily dose, prescribed daily dose values, and prescribed daily dose to defined daily dose ratio of antipsychotics prescribed.

No. of prescriptions (N=365)	Drug	ATC[a] code	DDD[b] (mg)	Median PDD[c] (mg)	Mean PDD (mg)	PDD (mg) 95% CI	Mean PDD/DDD[d]
17	Amisulpride[e]	N05AL05	400	800	811.76	652.4-971.1	2.03
37	Aripiprazole[e]	N05AX12	15	15	20.54	16.7-24.4	1.37
25	Asenapine[e]	N05AH05	20	10	14.4	11.3-17.5	0.72
11	Clotiapine[e]	N05AH06	80	40	35.45	24.4-46.5	0.44
11	Clozapine[e]	N05AH02	300	350	345.45	284.2-406.7	1.15
3	Fluphenazine[f]	N05AB02	1	0.89	1.19	0.61-1.78	1.19
7	Haloperidol[f]	N05AD01	8	5	7.63	2.4-12.9	0.95
3	Levomepromazine[f]	N05AA01	300	50	58.33	42.0-74.7	0.19
36	Olanzapine[e]	N05AH03	10	10	15.76	12.5-19.1	1.58
22	Paliperidone[f]	N05AX13	6	10.5	11.59	9.5-13.7	1.93
63	Long-acting paliperidone[f]	N05AX13	2.5	3.57	4.79	4.34-5.24	1.92
38	Quetiapine[f]	N05AH04	400	150	228.29	153.5-303.1	0.57
66	Risperidone[f]	N05AX08	5	6	7.61	6.5-8.7	1.52
1	Long-acting risperidone[e]	N05AX08	2.7	7.14	7.14	7.14-7.14	2.64
10	Tiapride[e,f]	N05AL03	400	300	290	244.3-335.7	0.73
1	Ziprasidone[f]	N05AE04	80	120	120	120.0-120.0	1.50
2	Zuclopenthixol acufase[f]	N05AF05	30	25	25	25-25	0.83
12	Zuclopenthixol depot[f]	N05AF05	15	9.5	10.3	8.8-11.9	0.69

[a]ATC: Anatomical Therapeutic Chemical.

[b]DDD: defined daily dose.

[c]PDD: prescribed daily dose.

[d]Mean PDD to DDD ratio.

[e]Oral administration.

[f]Injectable administration.

Discussion

Principal Findings

This study described a reproducible method for performing naturalistic prospective prescription analysis via a Web- and mobile phone–based application prototype, MEmind. This observational study was the first step in the development of a CDSS that may help care providers better monitor their prescriptions and make decisions regarding pharmacological treatment. In this study, we were able to identify polypharmacy, overly high dosage, and off-label use in a psychiatric inpatient setting. We found that APP was used in 35.8% of the patients in our 2 brief psychiatric inpatient units, with clozapine as the oral drug most used in APP and fluphenazine as the long-acting injection drug most used in APP. Antipsychotics were used mostly in schizophrenia spectrum and related psychotic disorders, but they were also prescribed in other nonpsychotic diagnoses. Risperidone and paliperidone, in both their oral and long-acting presentation, were the most prescribed antipsychotics. With respect to dosing, with the exception of only one prescription of long-acting risperidone, amisulpride was the antipsychotic prescribed at highest doses, whereas levomepromazine was the antipsychotic prescribed at lowest doses.

In our sample, the oral antipsychotics most used in APP regimen were clozapine, clotiapine, and amisulpride. One likely explanation for these findings regarding clotiapine in APP is that clotiapine is not principally used for its antipsychotic properties but rather for its hypnotic properties; this interpretation is supported by clotiapine's PDD/DDD ratio of 0.44. Clozapine was used in APP in 81.8% of cases. Out of 11 patients who were administered clozapine, 9 patients received pharmacological polytherapy and only 2 patients received monotherapy with a PDD/DDD ratio of 1.15. Amisulpride was

used in APP in 70.6% (12/17) of cases. Our use of these antipsychotics is consistent with their pervasive clinical use in our country [21] and worldwide [29].

Clinical guidelines recommend the use of clozapine in APP only for ultraresistant patients with schizophrenia [22]. This will reduce clozapine dose, minimize adverse effects and allow for the use of amisulpride APP to be the rule rather than the exception [29]. Moreover, a very common antipsychotic combination is the clozapine augmentation with amisulpride in patients with ultraresistant schizophrenia.

Long-acting antipsychotics were rarely used with first-generation antipsychotics but were used most frequently in APP. Second-generation antipsychotics, however, were used in pharmacological monotherapy and polytherapy in the same proportion. In our sample, long-acting paliperidone has replaced long-acting risperidone (used in only 1 patient) and is used in APP in almost 50% of cases. The use of paliperidone in this inpatient setting probably represents a fluctuation period during the hospitalization.

When observing the range of doses used in our sample, we noticed that the drugs used in higher doses were amisulpride (PDD/DDD = 2.03) as well as paliperidone in its long-acting presentation (PDD/DDD = 1.92) and oral presentation (PDD/DDD = 1.93). Both of these drugs are antipsychotics with a high affinity for dopamine D_2 receptor blockade. As a D_2 receptor binding of 70% is necessary for therapeutic benefits [30], high doses of these antipsychotics are commonly used to better reach this level of binding. Given that many patients arrive at inpatient settings with severe psychopathology, clinicians may attempt to use pharmacotherapies at higher dosages to stabilize patients in shorter amounts of time. On the other hand, levomepromazine, clotiapine, and quetiapine were the antipsychotics used at the lowest doses. Specifically, their PDD/DDD ratios were less than 0.5, which likely reflects levomepromazine and clotiapine being prescribed for nonpsychotic symptoms (such as insomnia or anxiety) and low doses of quetiapine being prescribed for bipolar depression [30].

Limitations

To improve acceptance among care providers, diagnoses were provided by psychiatrists rather than being obtained as the result of a structured clinical interview, such as the Structured Clinical Interview for DSM-5 (SCID-5). As shown in other studies, the implementation of EHRs or CDSSs may increase clinician workload [26]. In order to ease the burden and improve acceptance of the study procedure among clinicians, we did not include in the baseline assessment a structured interview of participants. This “as usual” approach of conducting is also consistent with the noninterventional setting of our study. However, to further assess the effect of implementation of the CDSS on patients’ clinical outcomes, a standard assessment will be performed in a forthcoming study.

In this study, we did not report the effect of MEmind on prescription habits. Changes in prescription behaviors have been reported by other studies describing the implementation of an e-prescribing tool [31]. It could have been of interest to report the effect of having instantaneous feedback from MEmind concerning off-label use. This, however, would have required a distinct methodology relying on a randomized controlled trial and a larger sample, which does not fit with a feasibility study.

Perspectives

This Web- and mobile phone–based application allows data gathering by both care providers and patients. The second phase of the project would be to combine clinical assessment with pharmacological insight. It may be especially relevant for patient monitoring after discharge, given that mHealth EMA is a promising method for reporting the clinical effects of pharmacological management. It will provide momentary assessment of the effects of a drug, including subjective perception of patients’ quality of life and health outcomes [7]. We will also be able to assess these features in the near future. These systems are able to explain how clinical practice is sometimes ahead of available evidence and may help develop better practices and security. At this point, we were able to provide information about drug management under real conditions and highlight points of conflict between ideal and real practice using the Web application. Our project may support the integration of mHealth techniques in prescription management systems and the development of future CDSSs.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Proportion of antipsychotic polypharmacy compared with monotherapy.

[PDF File (Adobe PDF File), 30KB - jmir_v19i1e25_app1.pdf]

Multimedia Appendix 2

Antipsychotic defined daily dose (DDD) when use in monotherapy versus polytherapy.

[PDF File (Adobe PDF File), 33KB - jmir_v19i1e25_app2.pdf]

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Abbreviations

APP: antipsychotic polypharmacy
ATC: Anatomical Therapeutic Chemical
CDSS: clinical decision support system
DDD: defined daily dose
EHR: electronic health record
EMA: ecological momentary assessment
mHealth: mobile health
PDD: prescribed daily dose

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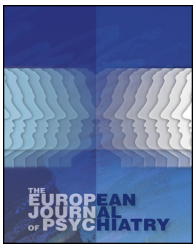

ORIGINAL ARTICLE

How far is clinical assessment from the bullseye? Using MEmind to compare clinical assessment with self-assessment in patients with depression and anxiety diagnosis

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KEYWORDS
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Anxiety disorders;
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Internet

Abstract
Background and objectives: Technology based assessments are being used for screening and monitoring in a wide scope of medical specialties, including mental health field. Depression and anxiety are common disorders in which e-health tools can be useful. We aimed to compare clinician assessment of illness severity in patients with depression and anxiety diagnosis with computer-based self-assessment within 24 h of clinician evaluation via MEmind (www.memind.net), a novel web-tool.
Methods: From May 2014, adult patients attended in outpatient settings in Fundación Jiménez Diaz Psychiatry Department were registered in MEmind, a web tool designed for psychiatric assessment. During the recruitment, clinicians use CGI-S for patient assessment via MEmind and provide patients a code and password to use the web-tool. We selected those patients diagnosed with depression and/or anxiety who connected within 24 h of the clinical visit and complete in the web page GHQ and WHO-5 scales. We calculated a bivariate correlation for CGI-S, WHO-5 and GHQ-12.
Results: Of the 231 participants, 157 (68%) were diagnosed with anxiety disorders and 74 (32%) with depression. Using the Spearman Rho test for correlation, we found a low correlation between CGI-S and total WHO-5 ($r = -0.192$; $p = 0.006$) and between CGI-S and total GHQ-12 ($r = 0.211$; $p = 0.002$) and a good correlation between total WHO-5 and total GQH-12 ($r = -0.606$; $p = 0.000$).
Conclusions: We found a low correlation between clinician assessment and patients' self-reports within 24 h of clinician evaluation. Factors that potentially influenced the degree of correlation related with patients, clinicians, measurements and technology are discussed.

Background

Technological developments and participatory health initiatives are expanding the scope of medicine from a traditional focus on disease cure to a personalized preventive approach.[1] Increasingly technology based assessments are being used for screening and monitoring in a wide scope of medical specialties. With this in mind, MEmind was developed to help clinicians optimize and personalize clinical psychiatric assessment and treatment.[2] Thereby, MEmind allows to improve communication among patients, support network and mental-health professionals; to monitor doctor's drugs prescription habits[3,4]; and monitoring patients through ecological momentary assessment (EMA).[5]

Anxiety and depression are common disorders, in fact more than 350 million people worldwide are affected by depression, making it the biggest cause of disability.[6] In 2010, the estimated number of persons affected by anxiety disorders and unipolar depression in Europe was 69.1 million and 30.3 million, respectively. Furthermore, depression represents 7.2% of the overall burden of disease, with 4,320,400 disability adjusted life years lost.[7]

An early diagnosis and treatment would result in improved personal functioning and reduce long-term costs.[8] Screening instruments for early diagnosis and monitoring are rarely used consistently; a technological approach could facilitate a consistent use. Combining validated screening instruments with the resourcefulness of tablet and phone applications that allow for EMA approaches offers the possibility to tackle these issues in a variety of settings, including primary care and specialty services.

In turn, clinical assessment, the tool to early diagnosis and optimal treatment in mental health, currently relies mostly on retrospective self-reports. The latter are inconsistent with interviewer judgments in as many as 60% of patients and correlate only modestly with informant reports (from clinicians or 7 friends/relatives).[9] Patients, caregivers and doctors may have differing perceptions of illness and yet

all potentially influence the evolution of that illness.[10] Even high-contact clinician ratings are retrospective, subject to recall bias, time-limited and mostly occur in a clinical setting, which might in itself influence the patients report and not reflect the patient's state in their actual environment.

Specifically, in cases of depression and anxiety, the agreement between patient self-assessment and clinician evaluation is far from be perfect. For depression, different studies find discrepancies in severity of illness depending on the rater (patient or clinician), with patients overrating their illness when compared with clinicians[11] whereas others find good correlation.[9,10] For anxiety, a good correlation is more frequently found.[12,13]

Ecological momentary assessment, by contrast, allows acquisition of self-reported information in real-time, maximizing accuracy and avoiding recall bias[14] and in this field is where we used the MEmind technology. Closely related to this, it is important to realize how new technologies are changing the doctor-patient relationship, nowadays it seems that ''people are more honest with their phones than with their doctors''.[15] Indeed, evidence supports that people are more forthcoming on online health questionnaires regarding sensitive areas of importance in psychiatry, such as past traumatic events like sexual abuse, substance abuse or suicidal thoughts and/or behavior.[16,17]

In this study our aim was to compare clinician assessment of illness severity in patients with depression and anxiety diagnosis with computer-based self-assessment within 24 h of clinician evaluation.

Methods

Participants and setting

Patients were recruited from psychiatric outpatient facilities within the catchment area of Fundación Jiménez Díaz General Hospital in Madrid. This hospital is part of the National Health Service and provides medical coverage to 850,000 people. From May 2014 onwards all clinicians working at the six mental health centers of the catchment area were encouraged to use the MEmind Wellness Tracker systematically in their clinical activity, after receiving specific training in its use.

Out of the total registered on the MEmind platform in the first year of use, 231 patients were included in the study. Inclusion criteria were based on timing of assessment and diagnosis, we included patients who submitted their self-assessment within 24 h of clinician assessment who were diagnosed with depression (ICD-10 codes F32 to F39) and/or anxiety (ICD-10 codes F40, F41 and F43).

Exclusion criteria were illiteracy, refusal to participate, current imprisonment, being under guardianship and emergency situations during which the patient's state of health did not allow for a written informed consent.

Materials: web tool and questionnaires

MEmind is available at www.memind.net and is compatible with Smartphones, Tablets and computers with any operating system. The MEmind application has two interfaces, one for clinicians (the *electronic health record view*) and another for patients (the *EMA view*).

The *electronic health record view* was designed for clinician use during medical, psychological or nurse practitioner visits. It was designed to capture data from standard psychiatric assessment including sociodemographic, diagnostic, treatment information as well as nurse practitioner annotations (e.g. vital signs and anthropometric measurements) organized in different tabs (Fig. 1). Additionally, care providers can add information to the basic evaluation using a large customizable choice of relevant scales or notes. For this study we used sociodemographic data and the Clinical Global Impression-Severity scale (CGI-S).[18]

The *EMA view*, designed for patients, consisted of three tabs with the following headings: (1) How are you today?; (2) General Health Questionnaire, and (3) Notes (Fig. 2). The first tab *How are you today?* included questions on eating and sleeping as well as the WHO (Five) Well-Being Index (WHO-5).[19] The second tab *General Health Questionnaire* consisted of the 12-Item General Health Questionnaire (GHQ-12).[20,21]

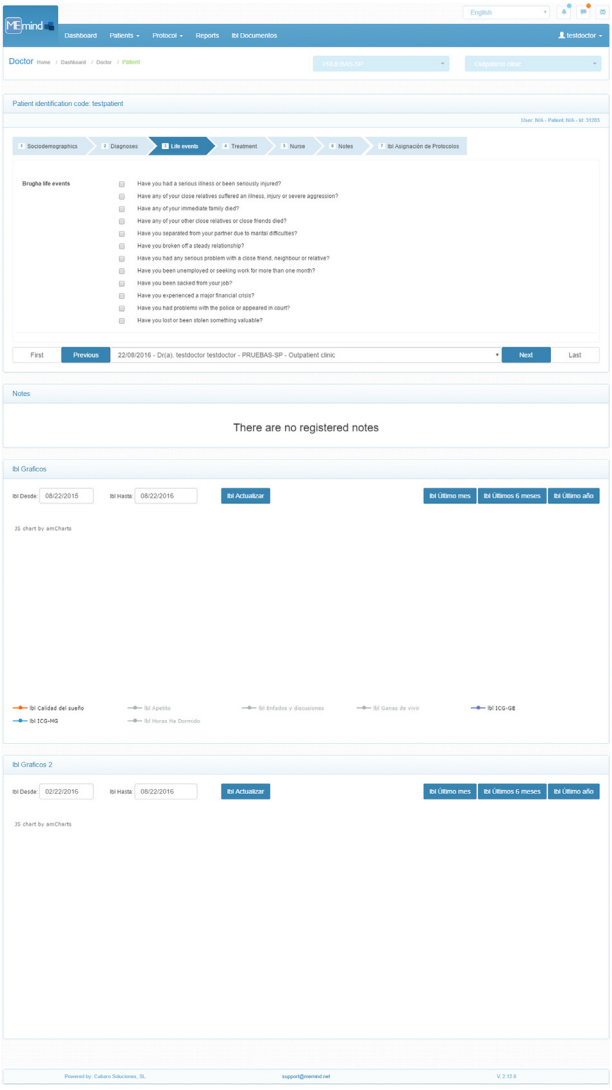

Fig. 1 MEmind Health Record View (P100).

Fig. 2 MEmind patient's view.

Finally, the third tab *Notes* allows free-text, but was not used in this study.

CGI-S rates the psychiatrist's impression of the severity of psychopathology ranging from 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients). WHO-5 is a scale with five items on the subjective quality of life based on positive mood, vitality and general interest. We used the percentage score method: a percentage score of 0 represents worst possible whereas a score of 100 represents best possible quality of life. GHQ-12 is the instrument most extensively used for screening common mental disorders, is composed of six positively phrased items[1,3,4,7,8,12] and six negatively phrased items.[2,5,6,9–11] Different scoring methods have been proposed for the GHQ items, we used standard GHQ–0011 scoring. According this method, for positive items 0 was given for answers ''more than usual'' and ''same as usual'' and 1 for answers ''less than usual'' and ''much less than usual''; and for negative items, 0 for answers ''not at all'' and ''no more than usual'' and 1 for answers ''rather more than usual'' and ''much more than usual''. All questionnaires were completed in Spanish.

Study procedure

Patients were informed about the study by the clinician during regular clinical visits. If the patient agreed to participate following written informed consent he/she was registered in the web tool and received username and password. During the visit, the clinician completed the CGI as well as other items in MEmind. Clinical diagnoses followed ICD-10 criteria.[22] Diagnoses were made after reviewing all available information, including medical records and clinical interviews with patient and relatives.

Once registered with MEmind, patients were able to connect to the EMA interface freely (no instructions were given regarding when and how often to connect). We selected those patients who connected and entered data (GHQ and WHO-5) within 24 h of the clinical visit.

Ethics and data protection

The study was conducted in compliance with the Declaration of Helsinki and approved by the local ethics committee. All participants gave written informed consent. Data protection was ensured and an external auditor guaranteed that security measures met the Organic Law for data protection standards at a high protection level.

Statistical analysis

We analyzed data using the SSPS version 22.0 package. First of all, with Kolmogorv–Smirnov test, we demonstrated a normal distribution for WHO-5 and a non-normal distribution for GHQ-12 and CGI-S. A descriptive analysis of sample characteristics was followed by a bivariate correlation (Spearman Rho test) for CGI-S, WHO-5 and GHQ-12.

Results

Descriptive findings

Out of the total number of patients registered by clinicians in MEmind during the first year of use in our outpatient facilities, 1288 used the EMA interface, of which 1106 did so within 24 h of the medical consultation. Of these, 231 were diagnosed with depression or/and anxiety disorders and were selected for inclusion in this study.

Of the 231 participants, 145 (62.8%) were women. Age of participants ranged between 18 and 72 years, with mean age of 43.7 years (sd = 12.2). One hundred and seven (68%) were diagnosed with anxiety disorders and 74 (32%) with depression.

Regarding the scales, CGI-S median score (25th and 75th percentiles) was 3 (3–4), the mean WHO-5 score was 44.83 (sd = 22.2) and the median GHQ-12 score (25th and 75th percentiles) was 4 (1–8) (for details on individual scale items see Fig. 3 and Tables 1 and 2).

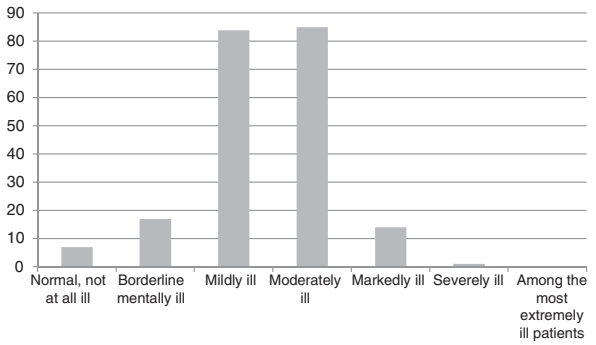

Fig. 3 ICG-S measured by the clinician.

Table 1 WHO-5 scores for individual items.

WHO-5 item		Mean (sd)
1	I have felt cheerful and in good spirits	47.14 (26.1)
2	I have felt calm and relaxed	45.88 (26.7)
3	I have felt active and vigorous	45.23 (28.6)
4	I woke up feeling fresh and rested	40.02 (30.4)
5	My daily life has been filled with things that interested me	45.89 (27.6)

Table 2 GHQ-12 scores for individual items.

GHQ-12 items		Score = 1	
		N	Percentage
1	Able to concentrate	148	64.1
2	Loss of sleep over worry	130	56.3
3	Playing a useful part	134	58
4	Capable of making decisions	147	63.6
5	Felt constantly under strain	125	54.1
6	Couldn't overcome difficulties	124	53.7
7	Able to enjoy day-to-day activities	132	57.1
8	Able to face problems	139	60.2
9	Feeling unhappy and depressed	133	57.6
10	Losing confidence	133	57.6
11	Thinking of self as worthless	150	64.9
12	Feeling reasonable happy	148	64.1

Correlation between clinician assessment of severity and self-reported scales

Using the Spearman Rho test for correlation, we found a low correlation between CGI-S and total WHO-5 ($r = -0.192$; $p = 0.006$) and between CGI-S and total GHQ-12 ($r = 0.211$; $p = 0.002$) and a good correlation between total WHO-5 and total GQH-12 ($r = -0.606$; $p = 0.000$).

Discussion

We found a low correlation between clinician assessment of severity illness and patients' self-reports using screening questionnaires within 24 h of clinician evaluation. Ideally, self-assessment would be equivalent to clinical assessment or at least have a good correlation; the results of this study indicate that in fact they do not. Several factors that potentially influenced the degree of correlation in this study are discussed below.

Factors related with patient

The *time factor* may have reduced the degree of correlation in different ways: Firstly, the time bias that a relatively broad time window of 24 h introduces, especially when considering the circadian variation of symptoms over time. Secondly, the assessment sequence i.e. the fact that all patients selected self-assessed after having seen the clinician may well have influenced their symptoms e.g. levels of anxiety or even just their symptom reporting. Also important is that users were using MEmind for the first time and this might also have influenced symptom reporting and anxiety levels.

The *self-selection* bias needs to be considered: only patients who actually completed the questionnaire within 24 h were included in the study. This might well include those who are more severely ill or simply more anxious about their symptoms, ultimately affecting levels of symptom reporting and in turn correlation. Alternatively it might have been those who felt unheard during clinicians visit and thus had an urge to convene the severity of their symptoms.

The variation in *setting* in which the self-evaluation took place: hospital, home or public transport to list a few may well influence patients' responses and attitudes toward the doctor. In line with this and also relevant is whether patients completed self-assessment on their own or in company of others.

Factors related with clinicians

The question of whether clinicians are failing to collect patient information accurately springs to mind. In the process of a clinical encounter a clinicians' role, among many, is to interpret idioms of distress to understand the complaint and diagnose. This process is inherently flawed and inevitably leads to a certain loss of information regarding the subjective symptom experience of patients. The holistic data collection system offered by MEmind and other such technologies might well serve to bridge this gap in current clinical practice.

More practical limitations inherent to the use of MEmind in the clinical setting as it is relatively time-consuming for clinicians during consultation complicate optimal data collection, the time point at which clinicians entered patients data might have varied possibly leading to recall bias.

Factors related with measures

Previous studies have questioned the validity of CGI. In a study evaluating the validity of the CGI-I and CGI-S as outcome measures in clinical trials, Forkmann et al.[23] found: (1) No strong evidence for the validity of neither of them; and (2) Congruence between CGI ratings from patients' and staff's perspective was not convincing. They concluded

that it could not be assumed that the view of the patient on the severity of his impairment was fully represented by therapist or team ratings. In fact they advocate for the incorporation of multiple self- and clinician-reported scales into the design of clinical trials in addition to CGI in order to gain further insight into CGI's relation to the patients' perspective. This finding could partly explain the reduced correlation observed between patient and clinician rating.

Factors related with technology

The role technology plays and its influence on peoples' behavior remains to be better understood. Patients might have had preconceptions regarding the implications of their entering of data electronically and so have altered their responses. However some evidence suggest that data collection over apps and other technologies apart from being more ecological and timely also enable people to respond more honestly.[15]

The strength of and need for a more holistic and integrative evaluation system such as the one MEmind offers becomes tangible when you consider our findings. Information goes amiss when evaluating patients purely from clinician visits and this affects patient management. Considering the impact on suicidal behavior, for example, the importance of the discrepancy between self and observer-rated depressive symptoms becomes more concrete. In a study by Tsujii et al. patients with mild major depressive disorder who overrated their depression severity as compared with clinicians' ratings were more likely to have a history of suicide attempts.[11]

The results of this study, which was part of the development of MEmind, reinforce the value of using a powerful novel tool for efficient data collection from a very large sample. In fact the size of the sample is one of the strengths of this study. MEmind is an EMA tool designed for the comprehensive evaluation of mental conditions; with easy access through any device with Internet connection (a mobile App will soon be available). Not only does MEmind have important implications for research in mental health, but also promises to be an effective aid in clinical practice.

Limitations inherent to the use of MEmind in the clinical setting is the fact that it is relatively time-consuming for clinicians during consultation, which may complicate optimal data collection.

In conclusion, our results highlight the importance of holistic evaluation systems that take patients and clinician assessments into account. Our web tool -MEmind- is a promising tool for this purpose. The experience gained using it has served to advance our understanding of the effects of using such a technology and become aware of the different factors that should be considered and potentially controlled for in research with these technologies.

Conflicts of interests

The authors have no conflict of interest to declare.

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Diagnostic Stability in Bipolar Disorder: A Narrative Review

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Learning objectives: After participating in this activity, learners should be better able to:
- Evaluate diagnostic stability in bipolar disorder
- Analyze the factors contributing to diagnostic stability

Objective: Diagnostic stability is the degree to which a diagnosis remains unchanged during follow-up. It is an important measure of predictive validity in bipolar disorder (BD). In this study, we review the literature concerning diagnostic stability in BD, analyze the factors contributing to diagnostic stability, and describe the implications of diagnostic boundaries and diagnostic delay.

Methods: A comprehensive literature search of MEDLINE and EMBASE databases was conducted, including all studies published from 1980 to 2016, to evaluate the diagnostic stability of BD. Thirty-seven articles were included: 6 focusing mainly on BD, 18 on psychotic disorders, 10 on depression, and 3 on diagnostic stability in psychiatric disorders in general. Data analysis was performed in standardized fashion using a predefined form.

Results: Despite a high variability of the methodological approaches taken, an acceptable degree of diagnostic stability was found. The most common criteria for evaluating diagnostic stability were prospective consistency and retrospective consistency. The mean prospective and retrospective consistencies were 77.4% and 67.6%, respectively. A large majority of studies were performed in Europe or in North America (67.5%), compared to 21.6% in Asia and only 10.8% in Africa, Oceania, and South America. Extreme ages, female gender, psychotic symptoms, changes to treatment, substance abuse, and family history of affective disorder have been related to diagnostic instability.

Conclusions: Several factors appear to have a negative impact on the diagnostic stability, but the evidence is insufficient to draw any robust conclusions. Nevertheless, despite variable prospective and retrospective consistencies, the overall diagnostic stability is good. Standardized methods need to be used to obtain more accurate assessments of stability.

Keywords: bipolar disorder, diagnostic change, diagnostic stability, prospective consistency, retrospective consistency

According to the 2013 Global Burden of Disease study, the number of cases of bipolar disorder (BD) increased by 50% in the 20 years prior to publication, reaching 50 million cases and thus making this disease the sixteenth leading cause of years lived with disability in 2013.[1] BD can have a major impact on an individual's ability to function and is associated with long-term risk of suicide.[2]

Diagnosis of psychiatric disorders, including BD, relies principally on cross-sectional assessment of clinical presentation. BD is a chronic and severe mental disorder characterized by recurrent episodes of depressed, elevated, and mixed mood. Moreover, as it is considered a lifelong illness, BD is likely to remain, once diagnosed, stable over time.[3] In clinical practice, however, a significant variation in diagnosis is observed.[4]

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In other branches of medicine, diagnoses are often supported by the identification of the underlying biological processes, whereas in psychiatry, diagnoses are based primarily on clinical syndromes.[5] In the absence of objective biological symptomatology, stability over time is the best means of validating BD diagnoses, and it can also be used to predict the course of the disorder.[6] For this reason, diagnostic stability may be used as a basis for the therapeutic management of BD patients. Conversely, the absence of stability in a diagnosis may have serious implications.[7]

The importance of obtaining accurate diagnoses of BD is of paramount importance. Underdiagnosis leads to delayed or ineffective treatment,[8] and overdiagnosis may also have adverse personal and social consequences, including unnecessary exposure to the risks of medication, missed opportunities for treatment of other conditions, and effects on work participation.[9] The rate at which bipolar patients receive inaccurate diagnoses in mental health facilities is estimated to be as high as 20%–60%.[10–12]

Though the number of studies focusing on diagnostic stability has increased in recent years, there remains a paucity of this type of research. Most of the published studies on diagnostic stability are focused on the first episode of psychosis and particularly on the subsequent consistency of schizophrenia diagnoses.[13] Other studies have used a meta-analytic approach to calculate the interrater reliability of BD diagnosis, as in the rigorous work by Santelmann and colleagues.[14,15] Studies focusing on BD diagnostic stability over time are scarcer. Diagnostic validity in psychiatric disorders requires stability over time, and because of the potential treatment implications, changes in diagnosis are a major issue to be considered.[16,17] In the case of BD, the literature is inconsistent. Some studies suggest moderate to high levels of temporal diagnostic stability of BD.[17–20] The initial diagnosis of BD, however, is often problematic. Diagnostic delays of 8 to 10 years are common, and studies consisting of repeated longitudinal evaluations have called into question the stability of this diagnosis in actual practice.[21–24]

Regardless of the great clinical and research implications of the issue of diagnostic stability of BD, this remains an understudied area.[5] Descriptions of the transition from diagnosis of depression and psychotic episodes to BD are of great interest and can be carried out by measuring the diagnostic stability of BD arising from such diagnoses. The aim of this study is to review the literature concerning diagnostic stability in BD, discuss the factors contributing to diagnostic stability, and describe the implications of diagnostic boundaries and diagnostic delay.

METHODS

Literature Search Strategy

A comprehensive literature search was conducted using the MEDLINE and EMBASE databases to search for texts published from 1980 to 2016. The keywords used for the search included the following: BD, manic-depression, mania, or bipolar spectrum AND diagnostic stability, diagnostic change, diagnostic consistency, diagnostic shift, diagnostic concordance, diagnostic conversion, and diagnostic progression. This keyword search was limited to the title and abstracts. The abstracts of the retrieved articles were then checked by applying the eligibility criteria. The PRISMA guidelines were followed to report findings.[25]

Inclusion Criteria and Retrieved Articles

Articles were included if they were published in English or Spanish, provided that they included adolescent (over 15 years of age) and adult cases, described a diagnostic shift from depression or psychotic episodes to BD, and informed the assessment of diagnostic stability for BD. Our definition of BD was not overly inclusive; we required that studies evaluate BD, psychotic episodes, or major depression (which included visits to the emergency department, inpatient hospitalization, and outpatient visits). Samples containing pediatric patients or pregnant women were not included. One study with patients younger than 15 years was included due to the low number of such patients (n = 20) in the total sample (n = 69,792). No studies in which the diagnoses were not performed by specialized mental health personnel were included. Cross-sectional, retrospective, and prospective studies were included. Citations within identified articles were included as additional sources. We omitted studies that included fewer than ten patients, uncompleted studies, conference abstracts, doctoral theses, and data not published in peer-reviewed journals. The initial electronic search identified 2317 documents. After evaluating the abstracts, we selected 37 articles that met the criteria (Supplemental Figure 1, available online at http://links.lww.com/HRP/A74). When selecting the articles, we were aware of unavoidable biases such as selection bias (differences between baseline characteristics of the groups) and detection bias (differences in how outcomes are measured). Thirteen studies (35%) included adolescent patients (>15 years). The selected studies are summarized in Table 1. The extraction of the pertinent data was standardized using a checklist based on PRISMA guidelines. Variables related to diagnostic stability were searched according to definitions appearing below.

Operative Definitions

Diagnostic stability is the measure of the degree to which a diagnosis remains unchanged during follow-up, providing a longitudinal means of validating the baseline diagnosis. It is based on the agreement of diagnoses over time and is irrespective of cross-sectional diagnosis at a single point of follow-up.[30] In a pioneering article published in 1970, Robins and Guze[16] mention diagnostic stability as one of the necessary criteria to verify the presence of a psychiatric syndrome, and for the first time the authors established a relationship with the predictive value of psychiatric diagnoses.

Prospective consistency (conceptually similar to positive predictive value) is the proportion of subjects in a diagnostic

Table 1

Narrative Review of Studies Examining Diagnostic Stability in Bipolar Disorders

Authors & year	Sample size/country	Study design & follow-up time	Inclusion criteria	Instruments	Results (95% confidence interval)
Studies focused on bipolar disorder					
Weeke et al. (1984)[4]	3062 Denmark	Retrospective 7 years	At least one manic-depressive diagnosis at admission Reassessed in second admission	ICD-8	RC: 20% (18.6–21.4)
Chen et al. (1998)[18]	936 (>18 years) USA	Prospective 7 years	At least four admissions Initial and final diagnosis schizophrenia or BD	DSM-III-R	PC: 70% (69.9–72.9) RC: 60% (56.9–63.1)
Kessing et al. (2005)[26]	4116 Denmark	Retrospective 9 years	Manic episode or BD Ten contact periods of assessment	ICD-10	PC: 68.8% (67.1–70.7)
Baca-Garcia et al. (2007)[21]	1153 Spain	Prospective 12 years	One BD diagnosis in at least ten assessments Multiple settings	ICD-10	PC: 49% (46.1–51.9) RC: 38% (35.1–40.8)
Ruggero et al. (2010)[17]	195 USA	Prospective 10 years	First admission due to psychosis At least one BD diagnosis in four assessments Consensus diagnosis	DSM-IV	PC: 79.6% (72.1–87.2) RC: 74.8% (66.8–82.7)
Ratheesh et al. (2015)[27]	52 Australia	Prospective 1 year	Meet Bipolar at Risk criteria (15–25 years, subthreshold manic symptoms and subthreshold depression in combination with either cyclothymic features or family history of BD)	DSM-IV	Diagnostic change to BD: 7.7% (0.4–14.9)
Studies focused on psychotic episodes					
Jorgensen et al. (1988)[28]	1136 Denmark	Retrospective 2 years	First admission with psychoses	ICD-8	PC: 72.9% (68.5–77.4)
Marneros at al. (1991)[29]	355 Germany	Historical prospective 25.2 years (mean follow-up)	One of the following episodes at least once: schizophrenic, melancholic, manic, manic-depressive mixed, schizodepressive, schizomanic and schizomanic-depressive mixed	DSM-III	PC: 62% (29.0–96.0)
Hollister et al. (1992)[24]	162 USA	Retrospective 3 years	Patients admitted four or more times	DSM-III-R	PC: 52.2% (37.7–66.6)
Fennig et al. (1994)[30]	278 USA	Prospective 6 months	First-admission psychotic patients Consensus diagnosis Baseline and 6-month assessments	DSM-III-R	PC: 85.7% (75.7–94.7) RC: 81.9% (71.7–90.8)

Table 1

Continued

Authors & year	Sample size/country	Study design & follow-up time	Inclusion criteria	Instruments	Results (95% confidence interval)
Studies focused on psychotic episodes					
Daradkeh et al. (1997)[31]	107 United Arab Emirates	Retrospective 2 years	>1 admission due to psychoses	ICD-10	PC: 87% (73.2–100.7)
Amin et al. (1999)[32]	168 UK	Prospective 3 years	First-episode psychosis Consensus diagnosis	DSM-III-R ICD-10	DSM-III-R PC: 78% (61.4–95.1) ICD-10 PC: 91% (77.9–103.0)
Schwartz et al. (2000)[3]	547 USA	Prospective 2 years	First-admission psychotic patients Baseline, 6-month, and 24-month assessments	DSM-IV	PC: 83% (76.8–89.2) RC: 84.8% (78.8–90.8)
Amini et al. (2005)[33]	48 Iran	Prospective 1 year	First episode of psychosis	DSM-IV ICD-10	PC: 100% RC: 94.4% (83.9–105.0)
Baldwin et al. (2005)[34]	194 Ireland	Prospective 6 months	First episode of psychosis	DSM-IV	PC: 97% (90.2–103.1)
Rufino et al. (2005)[22]	59 Brazil	Prospective 15 months	First psychotic episode Emergency setting 12-month minimal follow-up	DSM-IV	PC: 22.6% (7.9–37.3)
Schimmelmann et al. (2005)[35]	492 Australia	Retrospective 18 months	First-episode psychosis admitted patients 18-month reassessment	DSM-IV	PC: 83.2% (75.9–90.5) RC: 89.2% (84.3–96.3)
Whitty et al. (2005)[6]	147 Ireland	Prospective 4 years	First episode of psychosis Reassessed after four years	DSM-IV	PC: 80% (62.5–97.5)
Chang et al. (2009)[20]	166 China	Prospective 5 years	Young people with first-episode psychosis Consensus diagnosis	ICD-10	PC: 100% RC: 73.1% (56.0–90.1)
Bromet et al. (2011)[36]	470 USA	Prospective 10 years	First admission due to psychosis Consensus diagnosis	DSM-III-R DSM-IV	PC: 69.5% (60.2–78.7) RC: 58.4% (49.3–67.5)
Kim et al. (2011)[37]	150 Korea	Retrospective 15 years	At least one relapsed psychotic episode with admission Consensus diagnosis	DSM-IV	PC: 86.8% (76.1–97.6) RC: 64.7% (51.1–77.8)
Salvatore et al. (2011)[38]	517 USA	Prospective 2 years	Patients hospitalized in a first psychotic episode	ICD-10	Mania with psychosis PC: 99% (97.0–100.9) Mixed affective episode PC: 94.9% (91.4–98.3)

(Continued on next page)

Table 1

Continued

Authors & year	Sample size/country	Study design & follow-up time	Inclusion criteria	Instruments	Results (95% confidence interval)
Studies focused on psychotic episodes					
Heslin et al. (2015)[39]	505 UK	Prospective 10 years	First episode of psychosis Reassessment ten years later Consensus diagnosis	ICD-10 DSM-IV-TR	PC: 76.4% (65.1–87.6) RC: 67.7% (56.1–79.4)
Heslin et al. (2016)[40]	360 UK	Prospective 10 years	First episode of psychosis Reassessment ten years later Consensus diagnosis	ICD-10	PC: 97.1% (93.2–101.0) Diagnostic change to BD: 9.7% (2.9–16.6)
Studies focused on depression					
Coryell et al. (1995)[41]	932 USA	Prospective 5–10 years	In- and outpatients treated for affective disorders Older than 17 years IQ >70	RDC	Diagnostic change to BD: 10.2% (7.2–13.3)
Angst et al. (2005)[42]	406 Switzerland	Prospective 26 years	Inpatients with mania, endogenous depression, endoreactive depression, manic-depressive disorder, affective disorder with psychotic features including schizoaffective disorder	ICD-9	Diagnostic change to BD: 39.2% (33.7–44.6)
Gilman et al. (2012)[43]	6214 USA	Prospective 3 years	Diagnosis of MDD in the National Epidemiologic Survey on Alcohol and Related Conditions	DSM-IV	Diagnostic change to BD: 3.9% (3.4–4.4)
Li et al. (2012)[44]	2 cohorts: 1485 (2000–07); 2459 (2003–07) Taiwan	Prospective 8 years	All adult patients from the Nationwide Health Insurance database diagnosed with MDD by psychiatrists	ICD-9	Diagnostic change to BD 2000–07: 10.0% (8.5–11.5) Diagnostic change to BD 2003–07: 12.1% (10.8–13.4)
Dudek et al. (2013)[45]	122 Poland	Retrospective 30 years	Age >18 years at onset First established diagnosis of depression	ICD-9 ICD-10	Diagnostic change to BD: 32.8% (24.4–41.1)
Østergaard et al. (2014)[46]	8588 Denmark	Prospective 12 years	Patients assigned a diagnosis of psychotic depression from data from Danish registers	ICD-10	Diagnostic change to BD: 7.1% (6.5–7.6)
James et al. (2015)[47]	69,792 UK	Retrospective 4–12 years	Clinical diagnosis of depression from a linked data set of English national Hospital Episode Statistics	ICD-10	Diagnostic change to BD: 5.65% (5.4–5.8)

(Continued on next page)

Table 1

Continued

Authors & year	Sample size/country	Study design & follow-up time	Inclusion criteria	Instruments	Results (95% confidence interval)
Studies focused on depression					
Nakamura et al. (2015)[48]	89 Japan	Retrospective 9 years	Patients who were hospitalized for severe depression, both with and without psychotic episodes	ICD-10	Diagnostic change to BD: 12.3% (5.5–19.1)
Woo et al. (2015)[49]	250 Korea	Retrospective 5 years	Medical records of patients with a diagnosis of MDD without prior history of mania or hypomania	DSM-IV	Diagnostic change to BD: 18.4% (13.5–23.2)
Bukh et al. (2016)[50]	301 Denmark	Prospective 5 years	First-episode depression	ICD-10	Diagnostic change to BD: 8.6% (5.5–11.8)
Studies focused on psychiatric disorders in general					
Tsuang et al. (1981)[23]	445 USA	Prospective 30–40 years	Patients admitted for schizophrenia and affective disorders Consensus diagnosis	Feighner criteria	Interview form PC: 56.0% (35.5%–75.5%) Notes PC: 80.4% (64.0% to 96.8%)
Atwoli et al. (2012)[19]	114 Kenya	Prospective Turnaround time = 35 days	All admissions with at least one previous psychiatric admission	DSM-IV-TR	PC: 91.4% (82.1–100.7) RC: 69.6% (56.2–82.9)
Alavi et al. (2014)[51]	485 Iran	Retrospective 12 years	All admissions with at least one previous psychiatric admission	DSM-IV-TR	PC: 71% (66.9–74.9) RC: 69.4% (65.4–73.6)

BD, bipolar disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ICD, *International Classification of Diseases*; MDD, major depressive disorder; PC, prospective consistency; RC, retrospective consistency; RDC, Research Diagnostic Criteria.

category at first evaluation who received the same diagnosis at last evaluation. *Retrospective consistency* (conceptually similar to sensitivity) is the proportion of subjects in a diagnostic category at the last evaluation who were in that same category at baseline.[21,51,52] Cohen's kappa for interrater agreement measures the diagnostic agreement corrected by chance. Diagnostic agreement was interpreted according to Landis and Koch[53] (k < 0 absence of agreement, .10–.20 slight, .21–.40 fair, .41–.60 moderate, .61–.80 good, and .81–1 excellent).

RESULTS

In this review, we will briefly describe and compare the studies that have evaluated diagnostic shifts from depression or psychotic episodes to BD and that have informed the assessment of diagnostic stability for BD in the last 36 years (from 1980 to 2016). We selected 37 studies focused on diagnostic stability: 6 of them are mainly focused on BD,[4,17,18,21,26,27] 18 on psychotic disorders,[3,6,20,22,24,28–40] 10 on depression,[41–50] and 3 on diagnostic stability in psychiatric disorders in general.[19,23,51]

Most of the studies are prospective in design (n = 25; 67.5%), and 12 (32.4%) are retrospective. The main diagnostic criteria used were the *Diagnostic and Statistical Manual of Mental Disorders* (n = 17; 46%) and *International Classification of Diseases* (n = 15; 40.5%); three studies (8.1%) used both; one (2.7%) used the Research Diagnostic Criteria; and one (2.7%) used the Feighner criteria. Of the 37 included studies, 40 different assessment instruments were used to classify patients and symptoms. The most widely used criteria for diagnostic stability were prospective and retrospective consistency, which were used by 27 studies (73%). Less common measurement tools included the proportion of diagnostic change, used by 12 studies (32%), and Cohen's kappa for interrater agreement, used in 7 (19%).

Examining all 37 studies, we found a mean prospective consistency of 77.4% and a retrospective consistency of 67.6%. Because of the variability in samples sizes and in the relative importance of each group, we calculated the weighted mean for prospective and retrospective consistency in each diagnostic group, controlled by sample size (Table 2). By contrast, studies focusing on depression revealed a trend of diagnostic shifts to BD, with the consequence that prospective and retrospective consistencies cannot be assessed. Prospective and retrospective consistencies are summarized in Figure 1. A sizable majority of studies were performed in Europe or in North America (n = 25; 67.5%), whereas 21.6% (n = 8) were performed in Asia and 10.8% (n = 4) in Africa, Oceania, and South America. The sample sizes varied from 48 to 69,792 patients. Four studies (10.8%) had fewer than 100 patients; 25 (67.5%) had between 100 and 1000 patients; 7 (20%) had between 1000 and 10,000 patients; and 1 (2.7%) had more than a 10,000 patients. In describing the results of these studies, we focus on the most common criteria for diagnostic stability: prospective and retrospective consistency. A detailed summary can be found on Table 1.

Table 2

Weighted Means Controlled by Sample Size for Prospective and Retrospective Consistency in Each Diagnostic Group

Diagnostic group	Prospective consistency (95% CI)	Retrospective consistency (95% CI)
Bipolar disorders	65.7 (64.5–66.9)	32.9 (31.6–34.2)
Psychotic episodes	80.4 (79.4–81.4)	75.7 (74.1–77.3)
Psychiatric disorders in general	70.9 (68.6–73.2)	69.4 (65.8–73.1)

CI, confidence interval.

Studies Focused on BD

Six studies focused mainly on the diagnostic stability of BD throughout the evolution of the disease. These studies have highly variable consistencies, with an average retrospective consistency of 39.9% (95% confidence interval [CI], 38.7–41.3) and an average prospective consistency of 66.8% (95% CI, 65.4–68.1).

An analysis of the six studies reveals that two are retrospective studies, and the other four are prospective. The two retrospective studies (Weeke [1984][4] and Kessing [2005][26]) were conducted with large samples (n = 3062 and 4116, respectively) and for periods of seven and nine years, respectively. In both, the inclusion criteria required at least one manic-depressive diagnosis or one diagnosis of BD. In the study by Weeke,[4] 20% of the registry sample was retrospectively classified as bipolar. Kessing[26] had 56.2% BD diagnoses at first contact, with a 30% change during follow-up. The retrospective consistency varied from 20% to 30%. Kessing and colleagues[26] found that diagnostic delay was especially frequent among the young, though also in female patients.

Four studies (Chen [1998],[18] Baca-García [2007],[21] Ruggero [2010],[17] and Ratheesh [2015][27]) prospectively examined the stability of BD diagnoses. Two of these studies were conducted with large samples (Chen with n = 936 and Baca-García with n = 1153), whereas the populations included in Ruggero[17] (n = 195) and Ratheesh[27] (n = 52) were substantially smaller. Three of the studies lasted between 7 and 12 years, and only one lasted a year. The inclusion criteria were similar for three studies (at least one BD diagnosis or one manic-depressive diagnosis in several assessments), and one study evaluated the progression from other highly prevalent mental disorders to BD. The prospective consistency found in these studies was higher than the one found in retrospective studies focused on BD, with a difference varying between 49% (Baca-García) and 79.6% (Ruggero).

Ruggero and colleagues[17] found a high prospective consistency (79.6%). Two factors, however, may lead to inconsistent diagnoses among patients followed over several years:

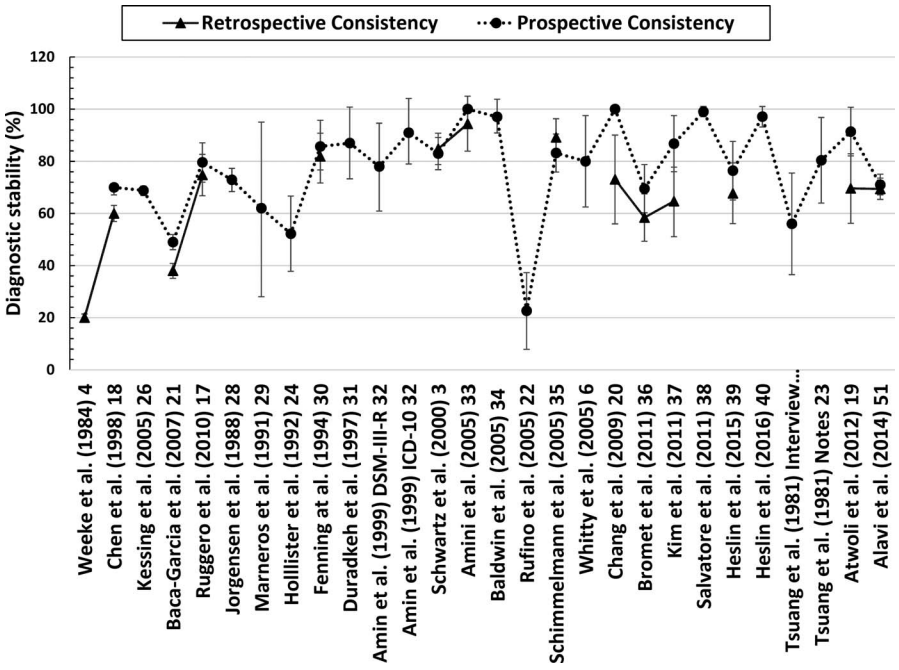

Figure 1. Diagnostic stability over time in studies including bipolar disorder patients. Error bars show confidence intervals at 95%.

(1) changes in the course of the underlying psychopathology, and (2) assessment errors. Even when using optimal assessment practices, a complex clinical presentation may make it difficult to accurately detect BD, resulting in increased odds of misdiagnosis over time. Baca-Garcia and colleagues[21] found a high prevalence of misdiagnosis and diagnostic shift from other psychiatric disorders to BD; additionally, temporal consistency was lower than in other studies (prospective and retrospective consistencies were 49% and 38%, respectively), and only 23% of patients received a BD diagnosis during >75% of the follow-up assessments.

Studies Focused on Psychotic Episodes

Eighteen studies examined the transition from psychotic episodes to BD, 13 of which are prospective, and 5 retrospective. Most of them focused on first psychotic episodes. The five retrospective studies were conducted by Kim[37] in 2011, Schimmelman[35] in 2005, Daradkeh[31] in 1997, Hollister[24] in 1992, and Jorgensen[28] in 1988. The samples varied from 107 to 1136 patients; four had follow-up periods of between 18 months and 3 years; and one had a follow-up period of 15 years.[37] For these retrospective studies, the average prospective and retrospective consistencies were 76.4% (95% CI, 73.4–79.5) and 76.9% (95% CI, 69.5–83.3%), respectively.

The other 13 studies were prospective in design, beginning with the first episode of psychosis. Two had a sample of 100 or fewer patients, and the other 11 ranged between 100 and 550. A study by Heslin[40] was excluded from analysis because it covered a similar population to the one described in another publication.[39] For these prospective studies, the average prospective and retrospective consistencies were 79.0% (95% CI, 75.9–82.2) and 76.7% (95% CI, 72.6–80.7), respectively. Bromet and colleagues[36] found that changes in symptoms and treatment were independent factors for diagnostic shifts.

Rufino and colleagues[22] found that psychotic disorder diagnoses made in an emergency room (ER) setting had high sensitivity but low specificity, and that BD showed the highest specificity. When the first diagnosis was made in an ER setting, kappa values were low when compared to the longitudinal follow-up diagnosis. By contrast, the agreement rates between diagnoses at ER discharge compared to follow-up diagnosis were satisfactory, with a kappa value of 0.57.

Studies Focused on Depression

Ten studies examined the evolution of the diagnosis from depression to BD. Six studies were prospective, and four retrospective. The four retrospective studies (Dudek [2013],[45] Nakamura [2015],[48] Woo [2015],[49] and James [2015][47]) were carried out with samples of 250, 89, 122, and 69,792 patients, with follow-up periods of 5, 9, 30, and 4 to 12 years, respectively. All reported the percentage of patients with diagnoses that shifted toward BD, which varied from 5.65%[47] to 32.8%.[45] James and colleagues[47] showed that 5.6% of depressed patients were eventually given a diagnosis of BD. The change to BD was more frequent in females, patients with higher age, and psychotic depression.

Within the prospective studies, sample sizes varied largely, ranging from 301[50] to 8588[46] patients. Most had a follow-up period between 3 and 12 years.[41–44,46,50] Angst's 2005 study[42] had a >20-year follow-up. All of them also reported

the percentage of patients that shifted their diagnoses toward BD, which varies from 3.9%[43] to 39.2%.[42]

Among patients with depression, a family history of affective disorder,[41,42] multiple depressive episodes,[42,46] psychotic symptoms,[41] treatment resistance,[44] and early age of onset[41,42,46] were found to increase the risk for conversion to BD. Other factors related to conversion to BD were living alone and receiving a disability pension.[46]

Boundaries of BD and Diagnostic Delay

Blacker and Tsuang[54] described BD as one of the most robust diagnostic entities in psychiatry, but some uncertainties are recognized. They identified a number of contested boundaries of the disorder, raising the question whether improved diagnostic criteria may be necessary for a number of research and clinical purposes.[54] The reasons that could demonstrate the distinct phenomenology of bipolar disorder include the following: its occurrence across history[55] and cultures,[56] its patterns of inheritance,[57,58] and its clear disturbance of physiologic function.[59]

The boundaries of BD remain unclear. Sara and colleagues[60] reported that diagnostic practice has changed in recent years, suggesting that diagnostic boundaries of BD are expanding in the Australian population, resulting in an 8% increase in BD prevalence—a trend that is accompanied by diagnostic change to other conditions. The change is observed in sensitive areas such as subclinical mood disorders, personality and affective disorders, and other mental pathologies such as psychotic events, substance use, and anxiety.

The time from disease onset to diagnosis is variable, though most authors suggest that significant delays are almost universal. Investigators from Harvard Medical School found that the mean time from the onset of BD symptoms to diagnosis was 9.6 years.[61] Hirschfeld and colleagues[62] found that at initial presentation, approximately 70% of patients were misdiagnosed and one-third received proper diagnosis only after 10 years.

DISCUSSION

Fifty million patients currently live with BD, a disorder ranked as the sixteenth leading cause of years lived with disability in 2013.[1] The diagnosis of BD relies principally on a cross-sectional evaluation of clinical features, though an accurate diagnosis can be reached only longitudinally. Diagnostic stability over time is the best source of evidence to validate the diagnosis of BD and predict its prognosis.[6] In addition, incorrect diagnoses have been reported in 20%–60% of cases,[10–12] and the retrospective diagnostic stability is reported as around 20%–38% in large series (>1000 patients).[4,21] Understanding the factors that determine diagnostic stability in BD may help improve prognosis.

To describe the factors related to diagnostic stability in BD, we performed a narrative review of the literature. The results were categorized based on the disorder preceding the BD diagnosis—mainly psychoses and affective disorders. Furthermore, data were grouped by study design for the sake of homogeneity and comparability.

There is no standard criterion to examine the diagnostic stability in BD; at least four different criteria are used, including prospective consistency, retrospective consistency, Cohen's kappa for interrater agreement, and proportion of diagnostic change. Taking into account only those that are used most frequently, here we observed very high variability. Symptom changes, the effects of treatments, the reinterpretation of clinical information, and the low reliability of diagnostic measures are some of the well-recognized factors of diagnostic stability.[3] Correct BD diagnoses take time to be established. Clinical polarities, social withdrawal, agitation, fluctuating symptoms, and concomitant substance abuse are commonly found in BD and may confound the clinical impression.[30,36] Due to the intrinsic nature of BD, there is no certainty of an accurate diagnosis.[18] Methodological changes are required to improve the way that diagnostic stability is measured. For example, a greater consensus on the use of data-collection instruments could improve the external validity of the results. In addition, other concepts such as *diagnostic reliability* have been used and could add value, bringing higher validity from a methodological and clinical perspective; interrater reliability is relevant because it measures the degree of agreement between two psychiatrists on the same diagnosis for the same patient.[14,15]

It is worth noting the large number of scales and the different diagnostic criteria used by the researchers, as this factor increased the variability of results and limited the ability to perform comparisons between studies. Since the methodological approaches, samples sizes, number of longitudinal evaluations, and population types for the 37 studies selected are so diverse, they cannot be compared directly. Additionally, the geographical distribution of the studies illustrates the importance of studying this topic outside Europe and North America to avoid cultural biases when interpreting results.

One of the greatest difficulties to be considered in prospective studies is the loss to follow-up, which alters prospective consistency. A low frequency of BD can be explained by transiently diagnosed patients with major depressive disorder who may evolve to BD.[63] The rate of BD misdiagnosis has been estimated at around 80% in a community sample[64] and 40% in sample of inpatients.[65]

In an attempt to assess the overall diagnostic stability for BD, we have calculated average prospective and retrospective consistencies, when available. We found a prospective consistency of between 75% and 80% and a retrospective consistency between 65% and 70%, which can be considered good diagnostic stability. This is consistent with two large meta-analyses by Santelmann and colleagues, which demonstrated that the reliability of BD diagnoses was good (kappa = .77; 95% CI, 0.73–0.82)[15] and excellent (kappa = 0.82; 95% CI, 0.77–0.86)[14] according to Landis and Koch's conventions for kappa values. Our assertion concerning consistency is biased, however, by the variability of the follow-up

times, which ranged from 35 days to 30 years (mean = 15.2 ± 6.7 years), methodological differences, and different clinical situations (selection and detection bias). Studies focused on patients with BD presented prospective consistencies between 50% and 80%, whereas studies focusing on psychotic episodes show prospective consistencies that reached 100%. This high diagnostic stability is derived from prospective studies with very small samples. When the studies with samples greater than 1000 patients were analyzed, a prospective consistency of around 65%–70% was found.

The fact that prospective stability is higher than retrospective stability is a reflection of daily clinical practice, where multiple manifestations or criteria sets are needed for the diagnosis of BD, resulting in delayed therapeutic interventions. Improving the detection of BD is of utmost importance for the clinician.

Recognizing the factors of diagnostic stability (and change) is crucial, as it could aid in understanding why diagnoses shift, thus providing clinicians with information on when to be alert to possible changes and consequently when to modify treatment.[39] In the 37 studies analyzed, we found several factors that influenced diagnostic stability and diagnostic delay. Younger age and female gender were risk factors for longer diagnostic delays[26] and for diagnostic changes from unipolar depression to BD.[47] Psychotic symptoms, changes in treatment, family history of affective disorder, early and older age of onset were also related to diagnosis instability. Another factor that should be mentioned is the presence of substance abuse. In several studies[26,27,51] it was reported as a modifier of clinical presentation, therefore leading to a misdiagnosis. Substance-related disorders are highly prevalent among psychiatric patients,[51] and in BD the rate is as high as 42%.[66]

In the light of our results, we suggest a high-risk clinical profile for diagnostic instability characterized by female gender, psychotic symptoms, changes in treatment, family history of affective disorder, and early or late age of onset.

The main limitation of this review concerns the selective use of assessment instruments and the criteria for diagnostic stability used on studies included. This means that the results are not comparable. As with all narrative reviews, some works may not have been included, because the search terms did not match any in the description or MESH terms, and causal analysis or meta-analytic assessment could not be performed.

Although a high diagnostic stability for BD has been reported in the literature, it is important to highlight that in daily clinical practice, the intervals between affective episodes is not yet completely understood, especially in cases of borderline personality disorder and type II BD. Additional work is needed to enhance diagnostic stability and to develop tools to quantify the risk of instability.

CONCLUSIONS

Based on our narrative review, we may tentatively draw some preliminary conclusions:

1. Diagnostic stability in BD is an understudied area, even though it represents the best means of validating the diagnosis of BD.
2. Improving the diagnosis of BD will result in early therapeutic interventions.
3. We propose a high-risk clinical profile for diagnostic instability: female gender, psychotic symptoms, changes in treatment, family history of affective disorder, and early or late age of onset of psychiatric manifestations.
4. High diagnostic stability for BD is frequently reported; daily practice is limited, however, in its ability to account for what occurs between affective episodes; additional research is needed.
5. To assess diagnostic changes, methods with higher methodological validity, such as Cohen's kappa for interrater agreement, should be used.

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Review article

Diagnostic stability of schizophrenia: A systematic review

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ABSTRACT

The objective is to systematically review previous literature on the diagnostic stability of schizophrenia, particularly to investigate prospective and retrospective consistency. We carried out a systematic literature search in PubMed and other minor sources from 1980 to July 2017. Specifically, prospective and retrospective consistency were examined. Thirty-nine studies were included, 5 focused on schizophrenia, 23 on psychotic episodes and 11 on psychiatric disorders in general. Samples sizes range from 60 to 10 058 subjects (total $N = 39\ 965$). The majority of studies ($n = 26$, 66.67%) were performed in Europe and North America and they had a prospective design ($n = 27$, 69.23%), with a median follow-up of 3 years. Prospective and retrospective consistency means were 84.29% and 67.15% respectively. Diagnostic change was also frequently measured ($n = 12$, mean 31.28%). The factors more commonly associated with diagnostic stability were: male sex, older age at the study inception, older age at onset, late stages of illness, family history of mental illness, poorer functioning and longer length of stay. Schizophrenia was found to have high diagnostic stability over time, although research on this topic is mainly focused in first psychotic episodes. More standardized methods are needed to further research diagnostic stability of schizophrenia over time and its determinants.

1. Introduction

Schizophrenia is characterized by chronic or recurrent symptoms of psychosis and impairments in social and occupational functioning (Fischer et al., 2017a). Schizophrenia has thus become a major cause of disability and economical burden due to direct and indirect costs according to the World Health Organization (Mathers et al., 2008; Murray and Lopez, 1996). However, its course and prognosis are considerably heterogeneous (from full symptomatic remission with positive outcome to presentations with continuous symptoms and poor outcome). Schizophrenia affects individuals across the world with a widely accepted prevalence of 1% internationally and an estimated cost more than $60 billion per year, including direct healthcare costs and indirect costs due to loss of productivity (Chong et al., 2016; Daradkeh, 1996; Fischer et al., 2017b; Insel, 2010; Nicholl et al., 2010; Owen et al., 2016; Simon et al., 2018; Vetter and Köller, 1993).

The diagnosis of schizophrenia is commonly made by exclusion since there are no pathognomonic symptoms and it is based on picking up features of psychosis from the diagnostic interview and collateral information (Fischer et al., 2017b). The psychiatric diagnoses in general, including that of schizophrenia, are therefore operationalized in the international taxonomies, in contrast to other areas of medicine (Fusar-Poli et al., 2016). In psychiatry, diagnoses are still based on the identification of the clinical syndrome (Chang et al., 2009) and the diagnostic criteria continue to rely on clinical features, outcomes and family history (Robins and Guze, 1970). Given the absence of biological markers, clinicians need to further verify clinical information for longer periods of observation over time (Chang et al., 2009; Ponizovsky et al., 2006). In 1938, Masserman and Carmichael (1938) followed-up a series of patients with schizophrenia and found that at twelve months a major

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revision of diagnosis was necessary in over 40% of them (Masserman and Carmichael, 1938). Concordance between clinicians, which is usually measured by the kappa index, has improved since the categorization of diagnostic criteria and so has improved the reliability of most diagnostic categories of mental disorders, although not as fully (Bousoño-García and Bousoño-Serrano, 2005; Ponizovsky et al., 2006). The utility of these diagnostic categories depend both on the inter-rater reliability and the temporal stability (Kendell, 2005; 1974). Diagnostic stability has been defined as the degree to which the original diagnosis is not changed at follow-up (Kendell, 1989), although diagnostic uncertainty and temporal instability are the rule rather than the exception in early psychosis (Chang et al., 2009). Diangostic stability is therefore a measure of predictive validity for psychiatric syndromes, although an under-studied area despite its clinical and research implications (Bromet et al., 2005; Chang et al., 2009; Forrester et al., 2001). On the other hand, several studies addressing diagnostic stability of first episode of psychosis diagnoses have been published, although the results were highly heterogeneous and diagnosis frequently changed to schizophrenia as shows a recent meta-analysis (Fusar-Poli et al., 2016). The method proposed by Robins and Guze (1970) was an outstanding initiative, although it is yet to be incorporated into routine clinical practice.

Within schizophrenia, evidence of diagnostic stability is fundamental to guide accurate early interventions. Its stability has been found very high in comparison to other clinical diagnoses in the medical field (Fusar-Poli et al., 2016). Moreover, schizophrenia appears to be a stable diagnosis from early phases of the illness (Pope et al., 2013), with higher stability over time than other psychosis spectrum disorders (Addington et al., 2006; Babigian et al., 1965; Forrester et al., 2001; Rice and Todorov, 1994), particularly higher than affective psychosis (Stanton and Joyce, 1993). These assertions have been confirmed by a recent meta-analysis on stability of first psychosis episodes (Fusar-Poli et al., 2016).

Schizophrenia is a very common and highly disabling mental disorder; however, early intervention can result in better outcomes. Hence, making an early diagnosis of schizophrenia (Nicholl et al., 2010) to be followed by a proper intervention (Flaum et al., 1992) is matter of major clinical relevance. Thus, the subject of diagnostic stability of schizophrenia merits further investigations in order to have a deeper understanding of this disorder, especially in the early stages of the illness, which could help clinicians to make more accurate diagnoses from the onset of the illness. Better understanding of diagnostic stability of this disorder will also improve the classification of first psychotic episodes, with the subsequent benefits to patients and their families. With this in mind, we aimed to conduct an up-to-date systematic review of the diagnostic stability of schizophrenia. Specifically, we hypothesized that while overall schizophrenia will have high levels of stability and some factors, namely being male, longer duration of untreated psychosis and more severe symptoms at first presentation will be associated with a more stable diagnosis whilst shorter studies will increase the likelihood of a diagnosis switch.

2. Material and methods

The methodology used in this review was similar to a previous work from our group on diagnostic stability of mental disorders and Bipolar Disorder (Baca-Garcia et al., 2007; Cegla-Schvartzman et al., 2018).

2.1. Search strategy

A systematic MedLine bibliography search was conducted using the following key-words: ("schizophrenia" OR "psychosis" OR "psychotic episode)" AND ("diagnostic stability" OR "diagnostic consistency" OR "diagnostic shift" OR "diagnostic change" OR "diagnostic progression" OR "diagnostic conversion" OR "diagnostic concordance"), which was restricted to the last 35 years (from 1980 to July 2017) and language (English or Spanish). Other sources were searched (MEDES and Google Scholar). References within identified articles were also included if they met the selection criteria below. Book chapters were excluded. The review complied with the PRISMA guidelines (Beller et al., 2013; Liberati et al., 2009; Moher et al., 2009; Urrútia and Bonfill, 2010). The statistical analysis was carried out using the R programming language (version 3.5.0) ("R: The R Project for Statistical Computing," 2019).

2.2. Selection criteria

Articles were included if the fulfilled the following selection criteria: 1) information on diagnostic stability of schizophrenia had to be available; 2) age: 15 years or older; 3) diagnosis: schizophrenia, psychotic episodes and other psychoses according to the ICD-9 (295.0–4, 295.8 and 295.9), ICD-10 (F20, F23, F29 and F22), DSM-III (295.10–35, 298.90 and 295.91–95), DSM-IV (295.9–40, 298.8) and DSM-V (295.40, 295.90, 298.8 and 298.9); 4) sample size larger than 10; 5) and only publications in peer-reviewed journals were considered.

2.3. Operative definitions

Diagnostic stability measures the extent to which a diagnosis remains unchanged over the follow-up, hence validating the baseline diagnosis and it is based on the concordance of diagnoses over time irrespective of potential further cross-sectional diagnoses over follow-up (Fennig et al., 1994). In 1970, Robins and Guze proposed diagnostic stability as one of the necessary criteria to confirm the presence of a psychiatric syndrome, which was also linked with the predictive value of psychiatric diagnoses, thus becoming a major innovation in psychiatry (Robins and Guze, 1970). Diagnostic stability is mainly assessed by Prospective and Retrospective Consistency.

Prospective consistency (PC) is the proportion of subjects in a category that maintain the same diagnosis at follow-up as at baseline, hence similar to Positive Predictive Value.

Retrospective consistency (RC, which is similar to Sensitivity) is the proportion of subjects in a category at follow-up who were in the same category at baseline (Addington et al., 2006).

3. Results

The initial search yielded 8121 references and 39 papers met the above predetermined selection criteria (Fig. 1 and Table 1). Seven studies (19.94%) included adolescents (age 15–17). The total sample of this review was n = 39 965. As shown in Table 1, out of the thirty-nine selected papers, 5 of them focused on schizophrenia (Chen et al., 1996; Dhossche and Ghani, 1998; Hwu et al., 1988; Munk-Jørgensen, 1985; Parnas et al., 2011), 23 works focused on psychotic episodes (or psychosis in general) (Addington et al., 2006; Amin et al., 1999; Amini et al., 2005; Baldwin et al., 2005; Bromet et al., 2011; Chang et al., 2009; Chinchilla et al., 1992; Crebbin et al., 2009; Fennig et al., 1994; Forrester et al., 2001; Haahr et al., 2008; Heslin et al., 2015; Jakobsen et al., 2007; Jørgensen and Mortensen, 1988; Kim et al., 2011; Kingston et al., 2013; Pope et al., 2013; Rahm and Cullberg, 2007; Salvatore et al., 2009; Schimmelmann et al., 2005; Schwartz et al., 2000; Subramaniam et al., 2007; Whitty et al., 2005) and 11 studies focused on psychiatric disorders in general (Atwoli et al., 2012; Baca-Garcia et al., 2007; Daradkeh et al., 1997; Daradkeh, 1996; Kim et al., 2011; Ponizovsky et al., 2006; Rabinowitz et al., 1994; Stanton and Joyce, 1993; Tsuang et al., 1981; Vetter and Köller, 1993; Woo et al., 2006).

The sample sizes of these studies ranged from 60 to 10 058 patients, with a total population of n = 39 965 (mean = 974.76, SD = 1774.24, media = 278). The vast majority of them (n = 26, 66.67%) were performed in Europe and North America, although there were also studies from Asia (n = 10, 25.6%) and Oceania (n = 2, 5.12%). Only one was performed in Africa (2.56%). The follow-up periods ranged from 5 months to 40 years (median = 3 years).

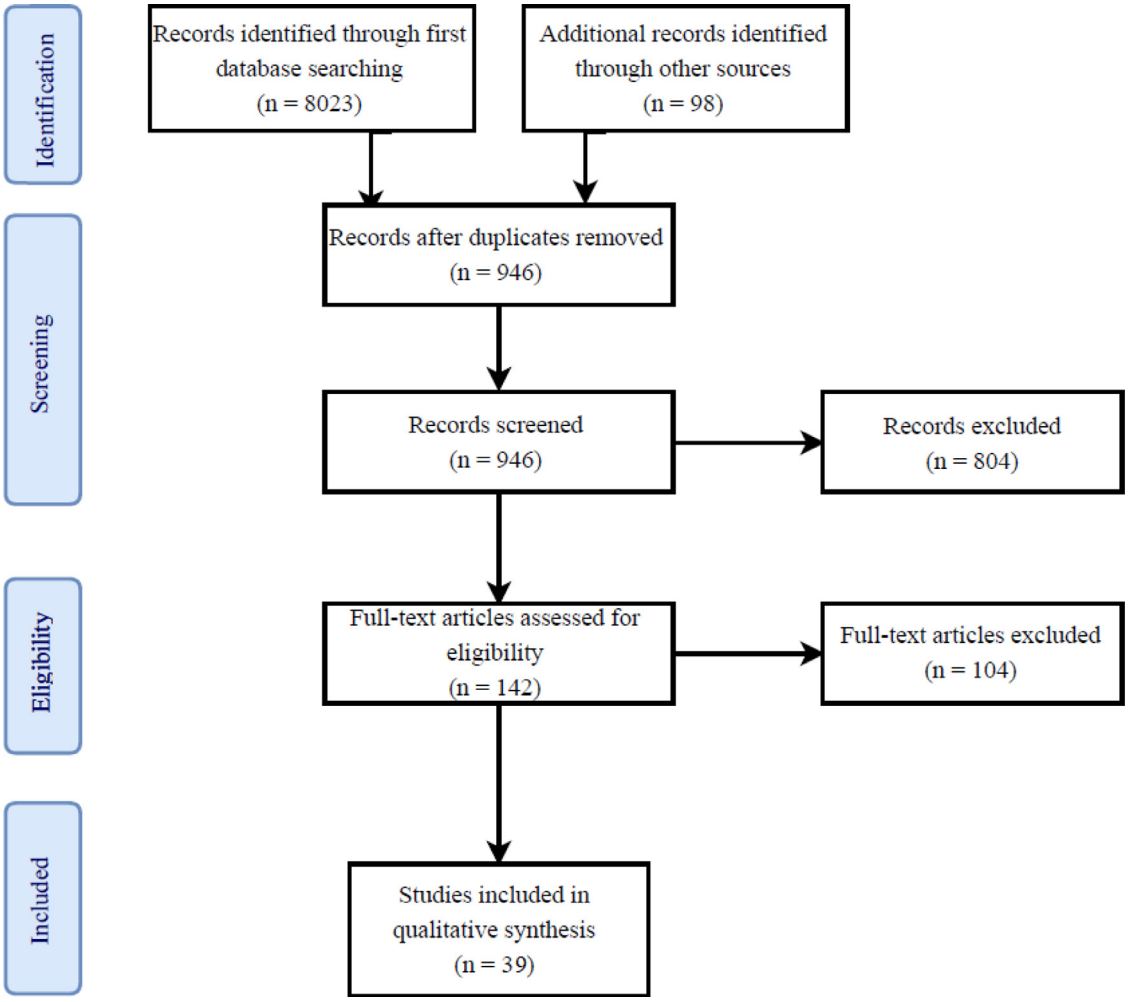

Fig. 1. Flow chart describing study selection during literature search.

Most of studies had a prospective design (n = 27, 69.23%) and used DSM-IV/DSM-IV-TR diagnostic criteria (n = 18, 46.15%).

In order to measure diagnostic stability PC was used in 32 studies (82.05%), while 15 of them also used RC (38.46%) (see Fig. 2). The proportion of diagnostic change to schizophrenia was used in 12 studies (30.76%), and in 5 of them it was the only measure of diagnostic stability. The Cohen´s kappa inter-rater reliability (n = 1, 2.56%) and the number of diagnostic changes (n = 1, 2.56%) were also taken as diagnostic stability measures by one study each. We based the description of the results on the prospective and retrospective consistency, which were the most common measures of diagnostic stability. We calculated simple means and SD. Furthermore, we completed the weighted means controlled for sample size given the high variation of samples sizes across studies and within each diagnostic group (Table 2). For PC, mean, SD and weighted mean are 84.29%, 11.21% and 76.81%; for RC, 67.15%, 13.05% and 54.09%. The mean proportion of diagnostic change was 31.28% (SD 19.34). These measures were not normally distributed.

3.1. Studies focused on schizophrenia

Five studies with schizophrenia samples were selected. Results in terms of diagnostic stability are shown in Table 2. Only one of these studies used RC, whilst the majority of them used the proportion of diagnostic change to schizophrenia, being the mean, SD and weighted mean 30.5%, 20.74 and 43.48% respectively. Three of them were prospective studies, while two of them had a retrospective design.

In the study of Parnas et al. (2011), changes of diagnosis were not related with baseline socio-demographic or psychopathological variables, other studies failed to replicate this. In Dhossche and Ghani (1998) diagnostic change to schizophrenia was associated with being female sex (i.e., women were more likely to be diagnosed with schizophrenia at the second visit). Furthermore, these two authors pointed out that the consensus in the diagnosis of schizophrenia was greater for males than for females, who tended to receive an affective disorder diagnosis prior to being diagnosed with schizophrenia, which also tended to occur later (Munk-Jørgensen, 1985). On the other hand, Chen et al. (1996) observed that more subjects had a diagnostic change to schizophrenia rather than schizophrenia being ruled out, which was more likely to occur in males and those from African o American origin.

The diagnostic stability of schizophrenia was moderate in the emergency room since it was an uncommon diagnosis at first admission (Dhossche and Ghani, 1998; Munk-Jørgensen, 1985), although most of the diagnostic changes were made in the early stages (Hwu et al., 1988).

3.2. Studies focused on psychosis and psychotic episodes

The majority of the selected studies fell under this group. Most of them assessed diagnostic stability using PC (n = 20, 86.95%), or RC (n = 10, 43.47%), as shown in Table 2. The mean diagnostic change to schizophrenia was 31.9%.

Several of these studies found schizophrenia to have high diagnostic stability levels (Addington et al., 2006; Amini et al., 2005; Baldwin

Table 1
Literature review of studies examining diagnostic stability in schizophrenia.

Authors & year Studies focused in schizophrenia	N Country	Study design & Follow up Time	Inclusion criteria	Instruments	Results (%)
Munk-Jørgensen (1985)	587 Denmark	Retrospective 10.7–11.7 years	At least one diagnosis of schizophrenia	ICD-8	PC: - Men: 51.6 - Women: 54.1 RC: - Men: 71.4 - Women: 64.4
Hwu et al. (1988)	127 Taiwan	Prospective 7 years	Hospitalized Functional psychosis	IDC-9 DSM-III	Diagnostic change to schizophrenia: -ICD-9: 9.4 -DSM-III: 8
Chen et al. (1996)	936 USA	Retrospective 7 years	Diagnosis of schizophrenia Inpatients	DSM-III	Diagnostic change to schizophrenia: 32.8
Dhossche and Ghani (1998)	2212 USA	Prospective 7 months	Emergency assessments of schizophrenia	DSM-III	Diagnostic change to schizophrenia: 50
Parnas et al. (2011)	155 Denmark	Prospective 5 years	Patients diagnosed with schizophrenia in the first admission <40 years	ICD-10	PC: 93
Studies focused in psychosis and psychotic episodes					
Chinchilla et al. (1992)	79 Spain	Prospective 46.4 months (mean)	Psychosis	ICD-9 DSM-III	Diagnostic change to schizophrenia: - ICD-9: 7.5 - DSM-III: 24
Fennig et al. (1994)	278 USA	Prospective 6 months	Hospitalized first admission patients	DSM-III-R	PC: 75.4 Diagnostic change to schizophrenia: 50
Jørgensen and Mortensen (1988)	2294 Denmark	Prospective 2 years	First admitted to a psychiatric hospital as in-patients Diagnosis of functional psychosis >15 years	ICD-8	PC: 74.6
Amin et al. (1999)	168 United Kingdom	Prospective 3 years	Population based cohort, first contact with psychiatric services	ICD-10 DSM-III-R	PPV: - ICD-10: 83 -DSM-III-R: 82
Schwartz et al. (2000)	547 USA	Prospective 2 years	First admissions initially diagnosed with psychosis	DSM-IV	PC: 91.7 RC: 73.1
Forrester et al. (2001)	204 UK	Retrospective 1 year	>/=2 admissions 18–55 years	ICD-9 ICD-10 DSM-III-R RDC Feighner Criteria	PC: 56.6–97.9
Amini et al. (2005)	60 Iran	Prospective 1 year	First psychostic episode inpatients 15–60 years old	ICD-10 DSM-IV	PC: - ICD-10: 100 - DSM-IV: - RC: - ICD-10: 100 - DSM-IV: 16.6
Baldwin et al. (2005)	194 Ireland	Prospective 6 months	First episode of psychosis	DSM-IV	PC: 100
Schimmelmann et al. (2005)	492 Australia	Prospective 18 months	First psychotic episode	DSM-IV	PC: 97.3 RC: 50.2
Whitty et al. (2005)	147 Ireland	Prospective 4 years	First psychotic episode	DSM-IV	PC: 96 RC: 71
Addington et al. (2006)	228 Canada	Prospective 1 year	Individuals 16–50 years old Non-affective, non-organic, first psychotic episode	DSM-IV	PC: 95 RC: 63 Diagnostic change to schizophrenia: 26
Jakobsen et al. (2007)	100 Denmark	Retrospective 1 year	Functional psychosis	ICD-10	Number of diagnostic shifts: 3
Rahm and Cullberg (2007)	146 Sweden	Prospective and retrospective 3 years	First psychotic episode 18–45 years	DSM-IV	PC: 83
Salvatore et al. (2009)	517 USA	Prospective 2 years	First psychotic episode	DSM-IV	PC: 75 Diagnosis change to schizophrenia: 12.5
Subramaniam et al. (2007)	154 Singapore	Prospective 2 years	Early psychosis diagnoses	DSM-IV	PC: 87 RC: 63.2
Haahr et al. (2008)	301 Norway and Denmark	Prospective 3 years	First psychotic episode 18–65 years	DSM-IV	PC: 85–99 Diagnostic change to schizophrenia: 72
Chang et al. (2009)	166 China	Prospective 5 years	First psychotic episode Consensus diagnosis	ICD-10	PC: 95.8 RC: 82.9
Crebbin et al. (2009)				IDC-10	

(*continued on next page*)

Table 1 (*continued*)

Authors & year Studies focused in schizophrenia	N Country	Study design & Follow up Time	Inclusion criteria	Instruments	Results (%)
	62	Prospective	> 16 years		Diagnostic change to
	UK	8 years	First episode of psychosis		schizophrenia: 20
Bromet et al. (2011)	470	Prospective	Consensus diagnosis	DSM-III-TR	PC: 89.2
	USA	10 years	First admissions	DSM-IV	RC: 53.0
					Diagnostic change to schizophrenia: 32
Kim et al. (2011)	150	Prospective	Readmissions for psychotic episodes after	DSM-IV	PC: 91.3
	Korea	15 years	first hospitalization for psychotic episode		RC: 90.3
Kingston et al. (2013)	202	Prospective	First psychiatric episode	DSM-IV	PC: 88
	Ireland	6 years	>/= 16 years		RC: 62
Pope et al. (2013)	214	Prospective	First psychotic episode	DSM-IV-TR	PC: 92.1
	Canada	1 year	14–30 years		Diagnosis change to schizophrenia: 43.1
Heslin et al. (2015)	557	Prospective	First psychotic episode	ICD-10	ICD-10:
	UK	10 years		DSM-IV-TR	-PC: 75.1
					-RC: 68.6
					DSM-IV-TR:
					-PC: 72.9
					-RC: 59.8
Studies focused in psychiatric disorders in general					
Tsuang et al. (1981)	525	Prospective	Admissions to hospital after first	Feighner	PC: 92.5
	USA	30–40 years	diagnosis	criteria	
Stanton and Joyce (1993)	3184	Retrospective	First admission	ICD-9	PC: 67
	New Zealand	5 years	15–65 years		Diagnosis change to schizophrenia: 10–15%
Vetter and Köller (1993)	267	Prospective	Inpatients	ICD-9	PC: 93
	Germany	12.5 years (mean)	Consensus diagnosis		
Rabinowitz et al. (1994)	2220	Prospective	Random first admissions	ICD-9	PC: 73
	Israel	9 years			
Daradkeh (1996)	312	Retrospective	In-patients	ICD-10	PC: 74
	United Arab Emirates	4 years	>1 admission		
Daradkeh et al. (1997)	107	Retrospective	In-patients	ICD-10	PC: 87
	United Arab Emirates	2 years			
Ponizovsky et al. (2006)	10 058 (3 cohorts of	Cross-sectional	Psychiatric admissions	ICD-9	PC:
	2996, 3021, 4041)	14 years	Diagnosis after discharge	ICD-10	- Cohort 1: 68.0
	Israel				- Cohort 2: 81.6
					- Cohort 3: 94.2
Woo et al. (2006)	934	Retrospective	Attended in emergency service and then	DSM-IV	ƙ:0.5
	USA	1 year	hospitalized		
Baca-Garcia et al. (2007)	10 025	Prospective	>18 years	ICD-10	PC: 69.6
	Spain	12 years	Assessed at least 10 times in multiple psychiatric settings		RC: 45.9
Kim et al. (2011)	472	Retrospective	Admitted to psychiatric ward	DSM-IV	PC: 86.9
	Korea	2 years	Diagnosis after discharge		RC: 75
Atwoli et al. (2012)	114	Cross-sectional descriptive	In-patients (at least one previous hospital stay)	DSM-IV-TR	PC: 75.9
	Kenya	Turnaround time during 5 months			RC: 87.2

SCZ: Schizophrenia. DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Text Revision. ICD-10: The International Classification of Diseases. PC: Prospective Consistency. RC: Retrospective Consistency. PPV: Positive Predictive Value. RDC: The Research Diagnostic Criteria.

et al., 2005; Bromet et al., 2011; Chang et al., 2009; Chinchilla et al., 1992; Fennig et al., 1994; Haahr et al., 2008; Heslin et al., 2015; Kim et al., 2011; Pope et al., 2013; Rahm and Cullberg, 2007; Salvatore et al., 2009; Schimmelmann et al., 2005; Schwartz et al., 2000; Subramaniam et al., 2007; Whitty et al., 2005), concluding that schizophrenia was a generally stable diagnosis (Kingston et al., 2013).

Those less likely to change a diagnosis of schizophrenia were women (Salvatore et al., 2009) and were significantly older than those with a diagnosis change (Addington et al., 2006); they had a longer duration of untreated psychosis (DUP) (Addington et al., 2006), and they were older age at study inception when there was a gradual onset (Addington et al., 2006; Salvatore et al., 2009). Also, these subjects had the longest length of hospitalization (Subramaniam et al., 2007).

The relationships between diagnostic stability and family history of mental illness and global assessment of functioning (GAF) were not significant, although they showed a trend (Jakobsen et al., 2007). Lower GAF disability scores were associated with diagnostic stability in another study (Subramaniam et al., 2007). Diagnostic instability was associated with an initial unconfirmed diagnosis, initial non-affective disorders and auditory hallucinations at first presentation (Salvatore et al., 2009).

Also, the majority of diagnostic shifts resulted in a diagnosis of schizophrenia (Addington et al., 2006; Bromet et al., 2011; Chang et al., 2009; Chinchilla et al., 1992; Crebbin et al., 2009; Fennig et al., 1994; Forrester et al., 2001; Heslin et al., 2015; Pope et al., 2013; Salvatore et al., 2009; Schimmelmann et al., 2005; Schwartz et al., 2000; Subramaniam et al., 2007). Moreover, Jørgensen and Mortensen pointed out that the number of patients diagnosed with schizophrenia increased at readmissions (Jørgensen and Mortensen, 1988). Other studies failed to find associations between stability and socio-demographic characteristics (Amin et al., 1999; Chang et al., 2009). Nevertheless, males (Haahr et al., 2008; Heslin et al., 2015), young age, black

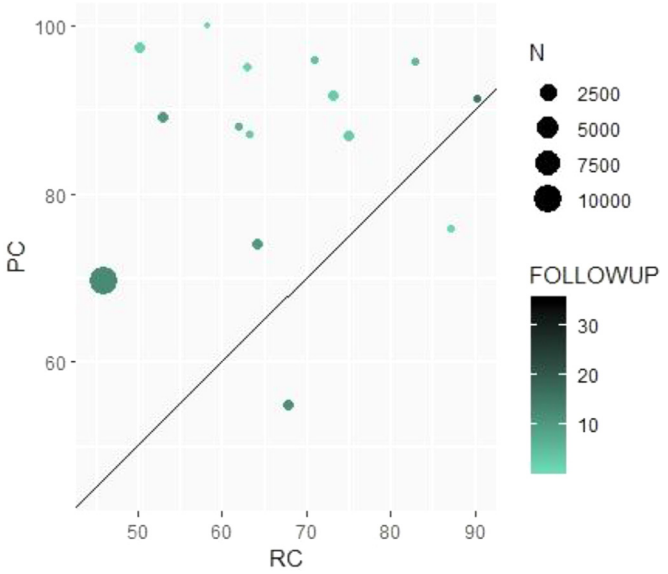

Fig. 2. Correlations between RC and PC in studies that calculated both variables. The oblique line corresponds with PC = RC, that is, if a point is above, then the study has PC > RC (stable and accumulating diagnosis), and the farther from the line the bigger the difference (PC-RC). We can see that the most common scenario corresponds with PC close to 90% and much bigger that RC (these are the points in the upper left corner. Low RC suggests that a significant number of patients may be diagnosed at baseline). Notice that the exceptions can be explained because the follow-up is particularly big (both PC and RC are close to 90%) (Kim et al., 2011) or the size is specially big (size approx. 10 000) (Baca-Garcia et al., 2007).

Table 2
Main results for diagnostic stability by group of studies and in global.

Studies focused in	Schizophrenia	Psychotic Episodes	General Psychiatric disorders	Global
PC				
Mean (%)	72.93	87.86	80.22	84.29
SD	28.38	8.83	10.22	11.21
Weighed mean (%)	61.25	83.20	75.48	76.81
RC				
Mean (%)	–	66.47	69.37	67.15
SD		12.09	21.22	13.05
Weighed mean (%)	–	64.04	47.64	52.09

SCZ: Schizophrenia. PC: Prospective Consistency. RC: Retrospective Consistency. SD: Standard Deviation.

Africans, being single (Heslin et al., 2015) and more academically and socially impaired at baseline (Bromet et al., 2011; Haahr et al., 2008; Heslin et al., 2015; Schimmelmann et al., 2005; Schwartz et al., 2000; Whitty et al., 2005) predicted a change of diagnosis to schizophrenia.

Longer duration of the initial episode and longer hospital stay were also associated with a change of diagnosis (Amin et al., 1999; Crebbin et al., 2009; Schwartz et al., 2000). However, mixed results were reported regarding DUP, which was the only predictor of a diagnosis shift in one study (Subramaniam et al., 2007). A diagnostic change towards schizophrenia was linked with longer DUP (Haahr et al., 2008; Heslin et al., 2015; Schwartz et al., 2000), although one study failed to replicate this (Chang et al., 2009). With regard to the effects of early substance abuse on diagnostic stability overall findings were inconclusive (Schwartz et al., 2000; Whitty et al., 2005).

Other factors associated with diagnostic shift towards schizophrenia were family history of psychotic illness (Chang et al., 2009); use of antipsychotics (Bromet et al., 2011; Schwartz et al., 2000); more negative symptoms and reality distortion (Bromet et al., 2011; Heslin et al., 2015; Schwartz et al., 2000) and psychopathological severity (Haahr et al., 2008; Schimmelmann et al., 2005; Whitty et al., 2005).

However, being diagnosed with bipolar disorder and having manic (Heslin et al., 2015) or depressive symptoms (Bromet et al., 2011) were associated with an unchanged diagnosis.

3.3. Studies focused on psychiatric disorders in general

Eleven selected studies reported on psychiatric disorders and diagnosis change towards schizophrenia, which was measured by PC except in one study, which used the Cohen´s Kappa inter-rater reliability (Woo et al., 2006).

Schizophrenia was found to be one of the most stable diagnosis (Daradkeh, 1996; Ponizovsky et al., 2006; Rabinowitz et al., 1994; Stanton and Joyce, 1993; Tsuang et al., 1981; Vetter and Köller, 1993; Woo et al., 2006), and stability tended to increase over time (Atwoli et al., 2012; Daradkeh et al., 1997).

In this group, the clinical setting predicted diagnostic stability, which was greater in in-patient settings (Baca-Garcia et al., 2007; Woo et al., 2006) and in those subject to legal restrictions, while it was lower in those with medical comorbidities (Woo et al., 2006). A baseline diagnosis of "schizophrenic" psychosis and prior hospitalization (Vetter and Köller, 1993) but not the number of previous admissions (Kim et al., 2011) increased the diagnostic stability of schizophrenia.

Although older age was associated with a less likely diagnostic change (Rabinowitz et al., 1994; Stanton and Joyce, 1993), there were no differences in age of onset (Kim et al., 2011). Sex had little effect on stability (Kim et al., 2011; Stanton and Joyce, 1993) and it was not related to diagnostic subtype, symptom severity or family history of psychiatric illness (Kim et al., 2011). Even though duration of course is a diagnostic criteria in schizophrenia (Vetter and Köller, 1993), stability was not affected by the duration of the illness (Kim et al., 2011).

On the other hand, instability was linked with a "first" diagnosis of schizophrenia within 1–2 months following a readmission (Stanton and Joyce, 1993); and a transfer of care during the inpatient episode (Stanton and Joyce, 1993).

The diagnostic change to schizophrenia was more common from affective psychosis (10–15%) (Stanton and Joyce, 1993) or delusional psychosis (Ponizovsky et al., 2006) than from all other diagnoses.

4. Discussion

We investigated diagnostic stability of schizophrenia on previous literature by conducting a systematic review, which included 39 studies and 39 965 participants. Overall, diagnostic stability of schizophrenia was found to be high (approximately 70–90%), although first presentation with psychosis was linked with increase diagnostic instability, as expected. These considerations suggest the need for better monitoring of these patients upon initial diagnosis (Nicholl et al., 2010), which may have implications on clinical management plans (Flaum et al., 1992), patient outcomes and service provision (Whitty et al., 2005).

Compared to other psychotic and non-psychotic psychiatric diagnostic categories, schizophrenia shows the highest rate of diagnostic stability in the majority of studies, or at least it is among the most stable diagnoses (Daradkeh, 1996; Ponizovsky et al., 2006; Rabinowitz et al., 1994; Salvatore et al., 2009; Stanton and Joyce, 1993; Tsuang et al., 1981; Vetter and Köller, 1993; Woo et al., 2006), which replicate the results of a recent meta-analysis on this topic (Fusar-Poli et al., 2016). This may have reflected some over-diagnosis of schizophrenia (Atwoli et al., 2012) and the schizophrenia diagnosis criteria themselves, though it could rather show that diagnosis criteria for schizophrenia are accurate, well known and established.

Interestingly, diagnostic stability is not commonly researched in other areas of medicine, although diagnostic stability of dementia was estimated at approximately 90% (Koepsell et al., 2013), with a 26.6% of diagnostic change for dementia (De Moraes and Bertolucci, 2017), which increased up to 45–67% for cognitive impairment (Anstey et al., 2013; Brodaty et al., 2012; Loewenstein et al., 2009), hence comparable with the diagnostic stability of schizophrenia.

4.1. Diagnostic stability in terms of PC and RC

There are no established criteria for diagnostic stability. The majority of the selected studies used PC and RC, and the proportion of diagnostic change, and more rarely the Cohen´s Kappa inter-rater reliability. Although there was heterogenity, most of the selected studies showed schizophrenia to have high diagnostic stability, in the line with our hypotheses (Addington et al., 2006; Amini et al., 2005; Daradkeh, 1996; Fennig et al., 1994; Kim et al., 2011; Pope et al., 2013; Schimmelmann et al., 2005; Schwartz et al., 2000; Stanton and Joyce, 1993; Woo et al., 2006).

The mean PC and RC were 84.29% (SD 11.21) and 67.15% (SD 13.05), respectively, with weighted means 76.81% and 54.09%, which shows that schizophrenia diagnoses tend to remain stable over the follow-up and that initial diagnoses of schizophrenia were relatively accurate (see Fig. 2). In the frame of clinical staging models (McGorry et al., 2006; Wood et al., 2011), lower RC may indicate that in early stages, symptomatology is mainly unspecific, and so it is expected to evolve as the illness does (Fusar-Poli et al., 2017; Millan et al., 2016). Thus, the change in diagnosis might be a part of the disorder rather than a flaw in diagnostic criteria and current taxonomies.

Diagnostic stability was found to be associated with: male sex (Dhossche and Ghani, 1998), older age (Addington et al., 2006; Rabinowitz et al., 1994), older age at onset (Addington et al., 2006), late stages of illness (Hwu et al., 1988), a family history of mental illness (Chang et al., 2009; Hwu et al., 1988), lower GAF (Jakobsen et al., 2007; Subramaniam et al., 2007) and longer hospitalization (Subramaniam et al., 2007). Also, the in-patient setting was linked with higher diagnostic stability (Baca-Garcia et al., 2007). However, the above relationships may be due to tautological issues since the diagnosis of schizophrenia in the clinical setting is commonly based on the presence of such factors. Regarding DUP, overall results were mixed, with both longer (Addington et al., 2006; Haahr et al., 2008) and shorter DUP (Chang et al., 2009; Subramaniam et al., 2007) being associated with increased diagnostic stability, which also increased over time (Daradkeh, 1996). In terms of sex, women tended to receive diagnosis of schizophrenia later (Munk-Jørgensen, 1985). In addition, at longer duration of the initial episode (Amin et al., 1999) and the presence of medical comorbidities (Woo et al., 2006) were related to diagnostic instability.

With regard to a diagnostic change to schizophrenia, being male (Chen et al., 1996; Haahr et al., 2008; Heslin et al., 2015; Salvatore et al., 2009), younger age (Salvatore et al., 2009), an African or American origin (Chen et al., 1996; Heslin et al., 2015), number of hospitalizations (Crebbin et al., 2009; Jakobsen et al., 2007), and days in hospital (Crebbin et al., 2009; Schwartz et al., 2000), poorer functioning as measured by the GAF (Bromet et al., 2005), less severe depressive symptoms (Bromet et al., 2005) and more significant negative symptoms (Bromet et al., 2005; Heslin et al., 2015; Schwartz et al., 2000), receiving antipsychotic treatment (Bromet et al., 2005; Schwartz et al., 2000), the first years of the illness (Haahr et al., 2008), poorer baseline functioning (Haahr et al., 2008; Heslin et al., 2015; Schwartz et al., 2000; Whitty et al., 2005) and symptomatic severity (Haahr et al., 2008; Whitty et al., 2005) made such change more likely. Two studies reported on the relationship between early substance abuse and diagnostic stability of schizophrenia, with conflicting findings (Schwartz et al., 2000; Whitty et al., 2005).

4.2. Study limitations

Although the results of the study do not differ from those found on previous literature, they reflect the relevant between-studies methodological differences, namely study design, sample size and population of origin, number of assessments over the study period, duration of follow-up, scales and instruments used, diagnosis criteria and statistical analysis, which hinder for direct comparisons. In addition, the cultural differences of the populations of the studies need to be considered when interpreting the results.

Measures of diagnostic change to or from schizophrenia is neglected in most of the studies. Factors associated with diagnostic shift, specially towards schizophrenia should be examined as it could be of real interest in the assessment of first psychotic episodes.

It is also remarkable that the number of studies focused on schizophrenia (n = 5, 12.8%) is limited, being less numerous than in the other groups.

4.3. Conclusion

Schizophrenia was found to be one of the most stable diagnosis (Daradkeh, 1996; Fusar-Poli et al., 2016; Rabinowitz et al., 1994; Stanton and Joyce, 1993; Tsuang et al., 1981; Vetter and Köller, 1993; Woo et al., 2006), and stability tended to increase over time (Daradkeh et al., 1997). On the other hand, factors related to longer and better assessment of patients (such as in-patient setting, longer duration of stay, number of hospitalizations, later stages of illness) led to a more accurate and stable diagnosis from early stages of the illness. Consequently, making an early precise diagnosis remains a goal yet to be achieved in the clinical practice.

Diagnostic stability of schizophrenia was found to be very high (Addington et al., 2006; Amini et al., 2005; Baldwin et al., 2005; Bromet et al., 2011; Chang et al., 2009; Chinchilla et al., 1992; Daradkeh, 1996; Fennig et al., 1994; Fusar-Poli et al., 2016; Haahr et al., 2008; Heslin et al., 2015; Kim et al., 2011; Pope et al., 2013; Rabinowitz et al., 1994; Rahm and Cullberg, 2007; Stanton and Joyce, 1993; Subramaniam et al., 2007; Tsuang et al., 1981; Vetter and Köller, 1993; Woo et al., 2006), particularly when compared to other psychiatric disorders. However, consensus criteria for diagnostic stability and validated tools for its measurement are needed, which may lead to further research on this topic. Specifically, longitudinal first-episode psychosis studies are warranted to better understand diagnostic changes from early stages of the psychotic illness and their contributing factors, thus improving patient clinical outcomes via preventing adverse effects of misdiagnosis.

Conflict of interest

The authors declare there are no conflict of interest in the making of this work.

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